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International application number: PCT/US04/043595

International filing date: 22 December 2004 (22.12.2004)

Document type: Certified copy of priority document

Document details:
Country/Office: US
Number: 10/832,811
Filing date: 26 April 2004 (26.04.2004)

Date of receipt at the International Bureau: 03 February 2005 (03.02.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

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APPLICATION NUMBER: ***10/832,811***
FILING DATE: ***April 26, 2004***
RELATED PCT APPLICATION NUMBER: ***PCT/US04/43595***

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Carina Cannizzaro et al.
Title: KINASE INHIBITORY PHOSPHONATE ANALOGS
Attorney Docket No.: 1692.306US1
Customer No.: 21186

PATENT APPLICATION TRANSMITTAL

MAIL STOP PATENT APPLICATION
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X Return postcard.
X Utility Patent Application under 37 CFR 1.53(b) comprising:
  X Specification (520 pgs, including claims numbered 1 through 116 and a 1 page Abstract).
  X Unsigned Combined Declaration and Power of Attorney (6 pgs).

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TOTAL CLAIMS	116-20	96	x 18.00 =	$1728.00
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KINASE INHIBITORY PHOSPHONATE ANALOGS

PRIORITY OF INVENTION

This application claims the benefit of priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application Serial Nos. 60/465588, 60/465594, 60/465465, and 60/465569, all filed April 25, 2003; and to U.S. Provisional Patent Application Serial Nos. 60/495382, 60/495685, 60/495527, and 60/495686, all filed August 15, 2003; and to U.S. Provisional Patent Application Serial Nos. 60/513956, 60/513925, 60/514368, 60/514207, 60/514115, 60/514324, 60/514330, and 60/513974, all filed October 24, 2003; and to U.S. Provisional Patent Application Serial No. 60/531932, filed December 22, 2003; and to U.S. Provisional Patent Application Serial No. 60/536054, filed January 12, 2004. The entirety of all Provisional Applications listed above are incorporated herein by reference.

FIELD OF THE INVENTION

The invention relates generally to phosphonate-containing compounds with kinase-inhibitory activity, *i.e.*, compounds that are kinase inhibitors.

BACKGROUND OF THE INVENTION

Improving the delivery of drugs and other agents to target cells and tissues has been the focus of considerable research for many years. Though many attempts have been made to develop effective methods for importing biologically active molecules into cells, both *in vivo* and *in vitro*, none has proved to be entirely satisfactory. Optimizing the association of the inhibitory drug with its intracellular target, while minimizing intercellular redistribution of the drug, *e.g.*, to neighboring cells, is often difficult or inefficient.

Most agents currently administered to a patient parenterally are not targeted, resulting in systemic delivery of the agent to cells and tissues of the body where it is unnecessary, and often undesirable. This may result in adverse drug side effects, and often limits the dose of a drug (*e.g.*, glucocorticoids and other anti-inflammatory drugs) that can be administered. By comparison, although oral administration of drugs is generally recognized as a convenient and economical method of administration, oral administration can result in either (a) uptake of the drug through the cellular and tissue barriers, *e.g.*, blood/brain, epithelial, cell membrane, resulting in undesirable systemic distribution, or (b) temporary residence of the drug within the gastrointestinal tract. Accordingly, a major goal has been to develop methods for specifically targeting agents to cells and tissues. Benefits of such treatment includes avoiding the general physiological effects of inappropriate delivery of such agents to other cells and tissues, such as uninfected cells.

Many of the current treatment regimes for cell proliferation diseases such as psoriasis and cancer utilize compounds which inhibit DNA synthesis. Such compounds are toxic to cells generally but their toxic effect on rapidly dividing cells such as tumor cells can be beneficial. Alternative approaches to anti-proliferative agents which act by mechanisms other than the inhibition of DNA synthesis have the potential to display enhanced selectivity of action.

In recent years it has been discovered that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene *i.e.* a gene that, on activation, leads to the formation of malignant tumor cells (Bradshaw, *Mutagenesis* **1986**, *1*, 91). Several such oncogenes give rise to the production of peptides which are receptors for growth factors. The growth factor receptor complex subsequently leads to an increase in cell proliferation. It is known, for example, that several oncogenes encode tyrosine kinase enzymes and that certain growth factor receptors are also tyrosine kinase enzymes (Yarden *et al.*, *Ann. Rev. Biochem.*, **1988**, *57*, 443; Larsen *et al., Ann. Reports in Med. Chem.* **1989**, Chpt. 13).

Receptor tyrosine kinases are important in the transmission of biochemical signals that initiate cell replication. They are large enzymes that span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor (EGF), and an intracellular portion that functions as a kinase to phosphorylate tyrosine amino acids in proteins and hence influence cell proliferation. Various classes of receptor tyrosine kinases are known (Wilks, *Advances in Cancer Research*, **1993**, *60*, 43-73) based on families of growth factors thath bind to different receptor tyrosine kinases. The classification includes Class I receptor tyrosine kinases comprising the EGF family of receptor tyrosine kinases such as the EGF, TGFα, NEU, erbB, Xmrk, HER and let23 receptors, Class II receptor tyrosine kinases comprising the insulin family of receptor tyrosine kinases such as the insulin, IGFI and insulin-related receptor (IRR) receptors and Class III receptor tyrosine kinases comprising the platelet-derived growth factor (PDGF) family of receptor tyrosine kinases such as the PDGFα, PDGFβ and colony-stimulating factor 1 (CSF1) receptors.

It is known that Class I kinases such as the EGF family of receptor tyrosine kinases are frequently present in common human cancers such as breast cancer (Sainsbury *et al.*, *Brit. J. Cancer*, **1988**, *58*, 458; Guerin *et al.*, *Oncogene Res.*, **1988**, *3*, 21 and Klijn *et al.*, *Breast Cancer Res. Treat.*, **1994**, *29*, 73), non-small cell lung cancers (NSCLCs) including adenocarcinomas (Cerny *et al.*, *Brit. J. Cancer*, **1986**, *54*, 265; Reubi *et al.*, *Int. J. Cancer*, **1990**, *45*, 269; and Rusch *et al.*, *Cancer Research*, **1993**, *53*, 2379) and squamous cell cancer of the lung (Hendler *et al.*, *Cancer Cells*, **1989**, *7*, 347), bladder cancer (Neal *et al.*, *Lancet*, **1985**, 366), oesophageal cancer (Mukaida *et al.*, *Cancer*, **1991**, *68*, 142), gastrointestinal cancer such as colon, rectal or stomach cancer (Bolen *et al.*, *Oncogene Res.*, **1987**, *1*, 149), cancer of the prostate (Visakorpi *et al.*, *Histochem. J.*, **1992**, *24*, 481), leukaemia (Konaka *et al.*, *Cell*, **1984**, *37*, 1035) and ovarian, bronchial or pancreatic cancer (European Patent Specification No. 0400586). As further human tumor tissues are tested for the EGF family of receptor tyrosine kinases, it is expected that their widespread prevalence will be established in further cancers such as thyroid and uterine cancer. It is also known that EGF type tyrosine kinase activity is rarely detected in normal cells, whereas it is more frequently detectable in malignant cells (Hunter, *Cell*, **1987**, *50*, 823). It has been shown more recently (W. J. Gullick, *Brit. Med. Bull.*, **1991**, *47*, 87) that EGF receptors that possess tyrosine kinase activity are overexpressed in many human cancers such as brain, lung squamous cell, bladder, gastric, breast, head and neck, oesophageal, gynaecological and thyroid tumors.

Accordingly, an inhibitor of receptor tyrosine kinases should be of value as a selective inhibitor of the growth of mammalian cancer cells (Yaish *et al. Science*, **1988**, *242*, 933). Support for this view is provided by the demonstration that erbstatin, an EGF receptor tyrosine kinase inhibitor, specifically attenuates the growth in athymic nude mice of a transplanted human mammary carcinoma that expresses EGF receptor tyrosine kinase but is without effect on the growth of another carcinoma that does not express EGF receptor tyrosine kinase (Toi *et al.*, *Eur. J. Cancer Clin. Oncol.*, **1990**, *26*, 722.) Various derivatives of styrene are also stated to possess tyrosine kinase inhibitory properties (European Patent Application Nos. 0 211 363, 0 304 493 and 0 322 738) and to be of use as anti-tumor agents. The *in vivo* inhibitory effect of two such styrene derivatives that are EGF receptor tyrosine kinase inhibitors has been demonstrated against the growth of human squamous cell carcinoma inoculated into nude mice (Yoneda *et al.*, *Cancer Research*, **1991**, *51*, 4430). Various known tyrosine kinase inhibitors are disclosed in a more recent review by T. R. Burke Jr. (*Drugs of the Future*, **1992**, *17*, 119).

Kinase inhibitors have valuable pharmacological properties and can be used, for example, as anti-tumoral drugs and as drugs against atherosclerosis. The phosphorylation of proteins has long been known as an important step in the differentiation and proliferation of cells. Phosphorylation is catalyzed by protein kinases that are divided into serine/threonine kinases and tyrosine kinases. The serine/threonine kinases include protein kinase C and the tyrosine kinases include PDGF (platelet-derived growth factor)-receptor tyrosine kinase and Bcr-Abl kinase.

Kinase inhibitors inhibit cellular kinases that are involved in disease states, for example, Bcr-Abl. Chronic myelogenous Leukemia (CML) is a hematological stem cell disorder associated with a specific chromosomal translocation known as the Philadelphia chromosome that is detected in 95% of patients with CML and 20% with acute lymphocytic leukemia (ALL). The molecular consequences of the translocation is the fusion of the abl protooncogene to the bcr gene resulting in the production of an activated from of Abl tyrosine protein kinase. The Bcr-Abl protein is capable of inducing leukemias in mice, thus implicating the protein as the cause of these diseases. As the tyrosine kinase activity of the Bcr-Abl protein is essential to its transforming ability, an inhibitor would be useful therapy for these disorders.

In addition, kinase inhibitors prevent the development of resistance (multi-drug resistance) in cancer treatment with other chemotherapeutic drugs or remove existing resistance to other chemotherapeutic drugs.

Two processes, the *de novo* formation of vessels from differentiating endothelial cells or angioblasts in the developing embryo (vasculogenesis) and the growth of new capillary vessels from existing blood vessels (angiogenesis), are involved in the development of the vascular systems of animal organs and tissues. Transient phases of new vessel formation (neovascularization) also occur in the adult body, for example, during the menstrual cycle, pregnancy or wound healing. On the other hand, a number of diseases are known to be associated with deregulated angiogenesis, for example, retinopathies, psoriasis, hemangioblastoma, hemangioma, and neoplastic diseases (solid tumors). The complex processes of vasculogenesis and angiogenesis have been found to involve a whole range of molecules, especially angiogenic growth factors and their endothelial receptors, as well as cell adhesion molecules.

Recent findings show that at the center of the network regulating the growth and differentiation of the vascular system and its components, both during embryonic development and normal growth and in a wide number of pathological anomalies and diseases, lies the angiogenic factor known as vascular endothelial growth factor (VEGF), along with its cellular receptors (*see* Breier, G., *et al.*, *Trends in Cell Biology 6*, 454-6 (**1996**) and the references cited therein).

VEGF is a dimeric, disulfide-linked 46-kDa glycoprotein and is related to platelet-derived growth factor (PDGF). It is produced by normal cell lines and tumor cell lines, is an endothelial cell-specific mitogen, shows angiogenic activity in *in vivo* test systems (*e.g.* rabbit cornea), is chemotactic for endothelial cells and monocytes, and induces plasminogen activators in endothelial cells, which are then involved in the proteolytic degradation of extracellular matrix during the formation of capillaries. A number of isoforms of VEGF are known that show comparable biological activity, but differ in the type of cells that secrete them and in their heparin-binding capacity. In addition, there are other members of the VEGF family, such as placenta growth factor (PLGF) and VEGF-C.

VEGF receptors are transmembranous receptor tyrosine kinases. They are characterized by an extracellular domain with seven immunoglobulin-like domains and an intracellular tyrosine kinase domain. Various types of VEGF receptor are known, *e.g.* VEGFR-1, VEGFR-2, and VEGFR-3.

A large number of human tumors, especially gliomas and carcinomas, express high levels of VEGF and its receptors. This has led to the hypothesis that the VEGF released by tumor cells could stimulate the growth of blood capillaries and the proliferation of tumor endothelium in a paracrine manner and thus, through the improved blood supply, accelerate tumor growth. Increased VEGF expression could explain the occurrence of cerebral edema in patients with glioma. Direct evidence of the role of VEGF as a tumor angiogenesis factor *in vivo* has been obtained from studies in which VEGF expression or VEGF activity was inhibited. This was achieved with antibodies that inhibit VEGF activity, with dominant-negative VEGFR-2 mutants that inhibited signal transduction, or with the use of antisense-VEGF RNA techniques. All approaches led to a reduction in the growth of glioma cell lines or other tumor cell lines *in vivo* as a result of inhibited tumor angiogenesis.

In addition, hypoxia, a large number of growth factors and cytokines, *e.g.* Epidermal Growth Factor, Transforming Growth Factor a, Transforming Growth Factor A, Interleukin 1, and Interleukin 6, induce the expression of VEGF in cell experiments. Angiogenesis is regarded as an absolute prerequisite for those tumors that grow beyond a maximum diameter of about 1-2 mm; up to this limit, oxygen and nutrients may be supplied to the tumor cells by diffusion. Every tumor, regardless of its origin and its cause, is thus dependent on angiogenesis for its growth after it has reached a certain size.

Three principal mechanisms play an important part in the activity of angiogenesis inhibitors against tumors: 1) inhibition of the growth of vessels, especially capillaries, into avascular resting tumors, with the result that there is no net tumor growth owing to the balance that is achieved between apoptosis and proliferation; 2) prevention of the migration of tumor cells owing to the absence of bloodflow to and from tumors; and 3) inhibition of endothelial cell proliferation, thus avoiding the paracrine growth-stimulating effect exerted on the surrounding tissue by the endothelial cells that normally line the vessels.

Inhibitors of cyclin-dependent kinases, *e.g.*, Alvocidib (US Patent No. 4,900,727; also known as flavopiridol) have been identified as a potentially useful therapeutic agents for a variety of cancers, including gastrointestinal and colon tumors, leukemias and myelomas (see, for example, *Intl. J. Oncol.*, **1996**, *9*, 1143).

Inhibitors of tyrosine kinases, including Bcr-Abl, *e.g.*, Gleevec, are useful for the treatment of chronic myeloid leukemia (CML), and potentially for treatment of other cancers that express these kinases, including acute lymphocytic leukemia (ALL) and certain solid tumors. Gleevec was approved for the treatment of inoperable and/or metastatic malignant gastrointestinal stromal tumors (GISTs).

Inhibitors of Flt3 tyrosine kinase, *e.g.*, CEP-701 (US Patent No. 4,923,986) and Midostaurin (US Patent No. 5,093,330), have potential utility for the treatment of a variety of cancers (*Cancer Res.*, **1999**, *59*, 10).

Inhibitors of MAP Erk kinase, *e.g.*, PD-184352 (U.S. Patent No. 6,251,943), have been identified as potentially useful therapeutic agents for a variety of oncological disorders, including colon, breast, pancreatic and non-small-cell lung cancers (see, for example, *Proc. Am. Soc. Clin. Oncol.*, **2003**, *22*, abstract 816).

Other kinase inhibitors, *e.g.*, doramapimod (U.S. Patent No. 6,319,921), have been identified as potentially useful therapeutic agents for the treatment of inflammatory diseases such as rheumatoid arthritis, psoriasis and Crohn's disease.

Other kinase inhibitors, *e.g.*, BAY-43-9006 (U.S. Publication No. 2002/0165394) have been identified as potentially useful therapeutic agents for a variety of cancers including gastrointestinal and colon tumors, leukemia and carcinoma (*Curr. Pharm. Design*, **2002**, *8*, 2269).

Cytokine receptors are critical for the development and homeostasis of immune cells. These receptors all require the cytoplasmic tyrosine kinase JAK3 for signaling (Changelian, P. S. *et al.*, *Science*, **2003**, *302*, 875). CP-690,550 (WO 02,096,909) is an orally available Janus kinase (JAK)-3 inhibitor, for the potential treatment of transplant rejection and psoriasis.

Thus, there is a need for therapeutic agents that are kinase inhibitors with improved pharmacological properties, *e.g.*, drugs having improved kinase-inhibitory activity and pharmacokinetic properties, including improved oral bioavailability, greater potency and extended effective half-life *in vivo*. Such inhibitors would have therapeutic potential as, *e.g.*, anticancer agents. Such kinase inhibitory compounds may be used to treat breast cancer, non-small cell lung cancers (NSCLCs), adenocarcinomas, squamous cell cancer of the lung, oesophageal cancer, gastrointestinal cancer, colon cancer, rectal cancer, stomach cancer, prostate cancer, leukaemia, ovarian cancer, bronchial cancer, pancreatic cancer, thyroid cancer, uterine cancer, brain cancer, lung squamous cell cancer, bladder cancer, gastric cancer, head and neck cancer, gynaecological and thyroid tumors, to prevent the development of resistance (multi-drug resistance) in cancer treatment with other chemotherapeutic drugs or remove existing resistance to other chemotherapeutic drugs, retinopathies, hemangioblastoma, hemangioma, and neoplastic diseases, gliomas, to inhibit tumor angiogenesis, myelomas, chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL), inoperable and/or metastatic malignant gastrointestinal stromal tumors (GISTs), treatment of inflammatory diseases such as rheumatoid arthritis, Crohn's disease, treatment of cell proliferation diseases, and for the treatment of transplant rejection and psoriasis.

New kinase inhibitors should have fewer side effects, less complicated dosing schedules, and be orally active. In particular, there is a need for a less onerous dosage regimen, such as one pill, once per day.

Assay methods capable of determining the presence, absence or amounts of kinase inhibition are of practical utility in the search for inhibitors as well as for diagnosing the presence of conditions associated with kinase activity.

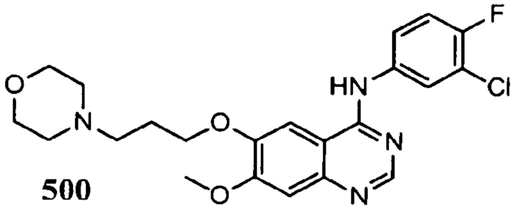
SUMMARY OF THE INVENTION

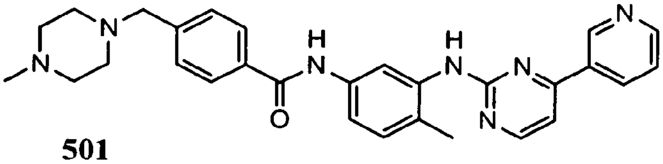
Intracellular targeting may be achieved by methods and compositions that allow accumulation or retention of biologically active agents inside cells. The present invention provides novel analogs of kinase-inhibitory compounds. Such novel kinase-inhibitory analogs possess all the utilities of the kinase-inhibitory compounds and optionally provide cellular accumulation as set forth below. In addition, the present invention provides compositions and methods for inhibition of kinases or therapeutic activity against kinases.

The present invention relates generally to the accumulation or retention of therapeutic compounds inside cells. The invention is more particularly related to attaining high concentrations of phosphonate-containing molecules in target cells. Such effective targeting may be applicable to a variety of therapeutic formulations and procedures.

Compositions of the invention include kinase-inhibitory compounds having at least one phosphonate group. Accordingly, in one embodiment the invention provides a conjugate comprising a kinase inhibiting compound linked to one or more phosphonate groups; or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, the invention provides a compound of any one of formulae **500-511**:


500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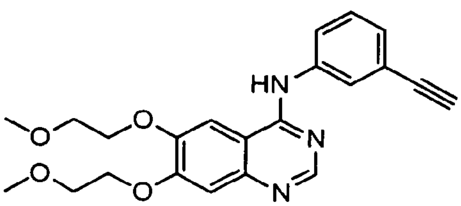
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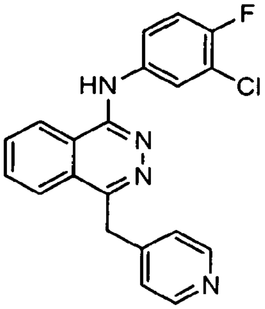
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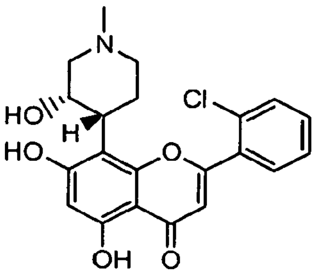
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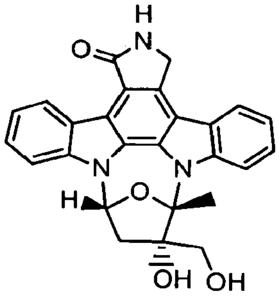
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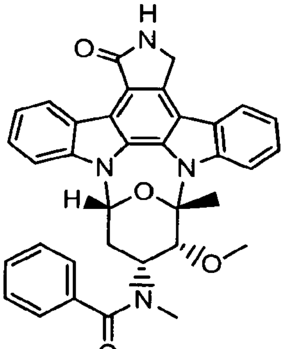
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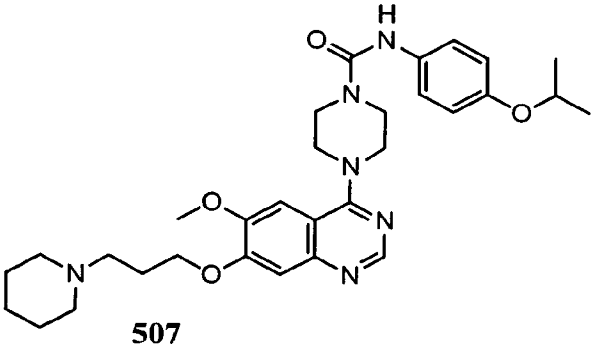
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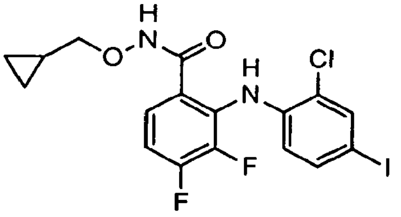
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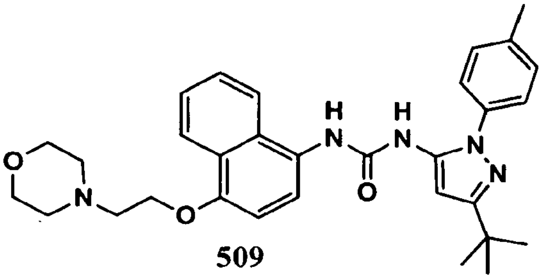

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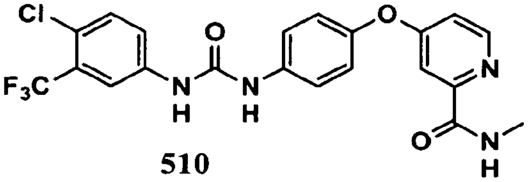

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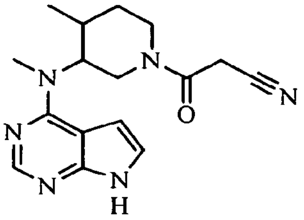


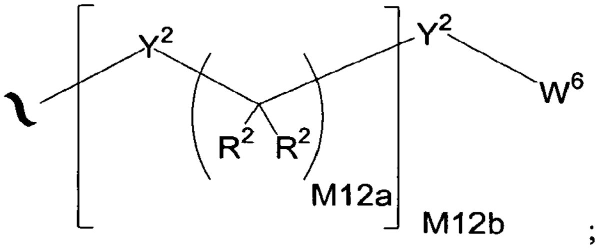
511

that is substituted with one or more groups A^0,

wherein:

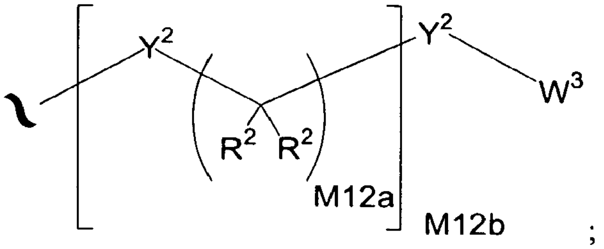
A^0 is A^1, A^2 or W^3 with the proviso that the conjugate includes at least one A^1;

A^1 is:

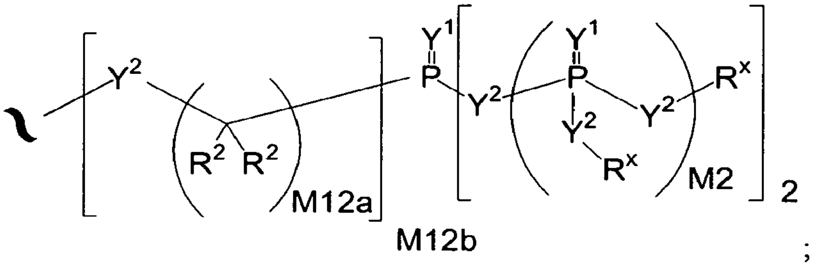

Y2
R2
R2
M12a
M12b
Y2
W6

;

A^2 is:


Y2
Y2
W3
R2
R2
M12a
M12b
;

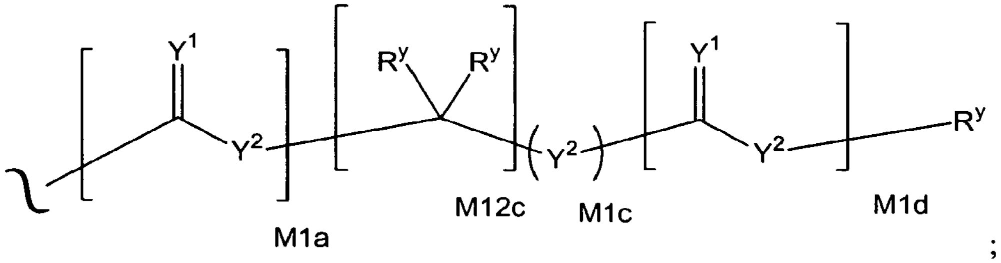
A^3 is:


Y2
R2
R2
M12a
M12b
Y1
P
Y2
Y1
P
Y2
Rx
Y2
Rx
M2
2
;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$; and when Y^2 joins two phosphorous atoms Y^2 can also be $C(R^2)(R^2)$;

R^x is independently H, R^1, R^2, W^3, a protecting group, or the formula:


Y1
Y2
M1a
Ry
Ry
M12c
Y2
M1c
Y1
Y2
M1d
Ry
;

wherein:

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_{M2}R^5$, or $-SO_{M2}W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1; and

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12

In another embodiment, the invention provides a compound of the formula:

$$[DRUG]-(A^0)_{nn}$$

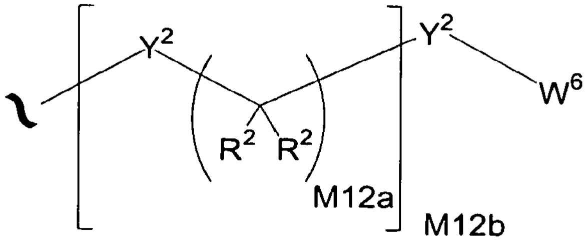
or a pharmaceutically acceptable salt or solvate thereof wherein,

DRUG is a compound of any one of formulae **500-511**;

nn is 1, 2, or 3;

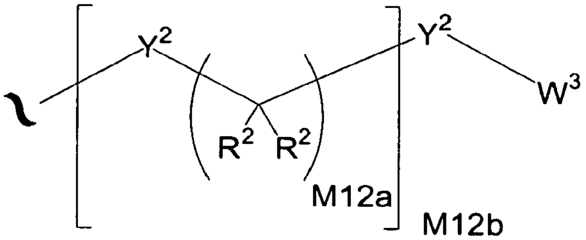
A^0 is A^1, A^2 or W^3 with the proviso that the conjugate includes at least one A^1;

A^1 is:


Y2
Y2
W6
R2
R2
M12a
M12b

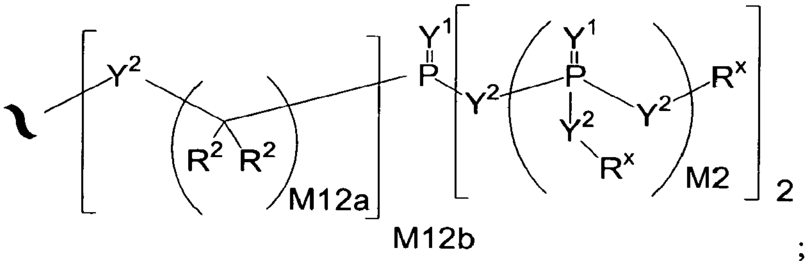
;

A^2 is:


Y2
Y2
W3
R2
R2
M12a
M12b

;

A^3 is:

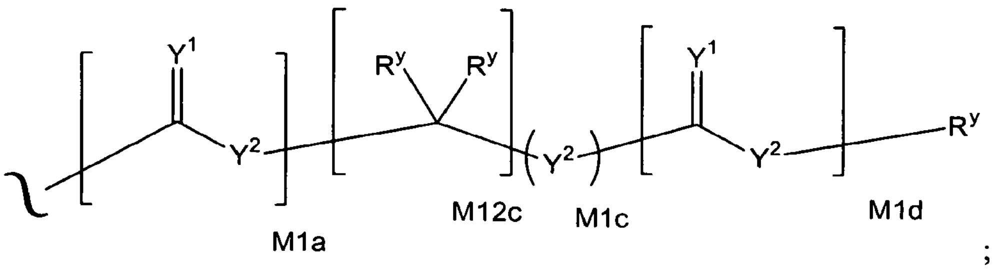

Y2
Y1
P
Y2
Y1
P
Y2
Rx
Y2
Rx
R2
R2
M12a
M12b
M2
2

;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$; and when Y^2 joins two phosphorous atoms Y^2 can also be $C(R^2)(R^2)$;

R^x is independently H, R^1, R^2, W^3, a protecting group, or the formula:


Y1
Y2
Ry
Ry
Y2
Y1
Y2
Ry
M1a
M12c
M1c
M1d

;

wherein:

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_{M2}R^5$, or $-SO_{M2}W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

M2 is 0, 1 or 2;

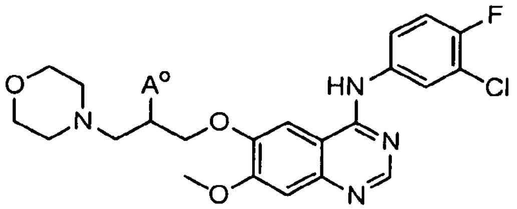
M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1; and

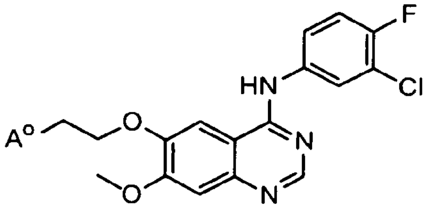
M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

In another embodiment, the invention provides a compound of any one of formulae **1-36:**



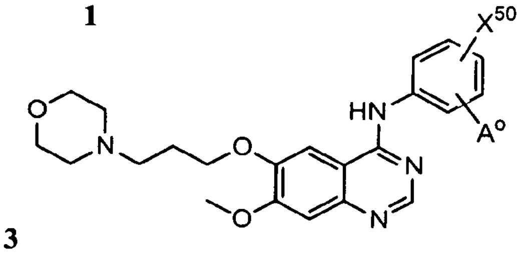
Aº
HN
F
Cl
O
N
O
N
N
O

1



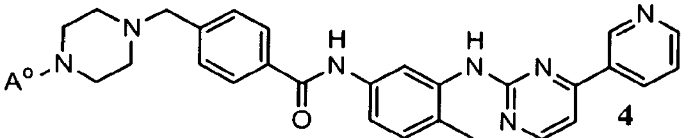
F
HN
Cl
Aº
O
N
O
N

2



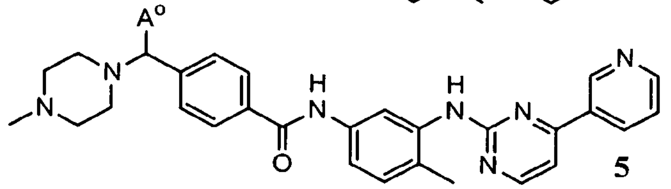
X50
HN
Aº
O
N
O
N
O
N

3



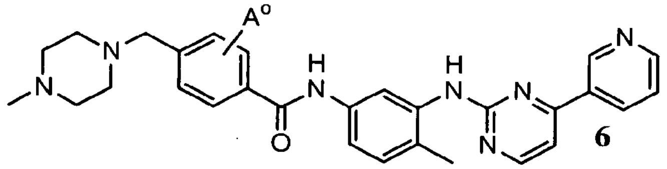
N
H
H
N
N
N
Aº
N
O
N

4



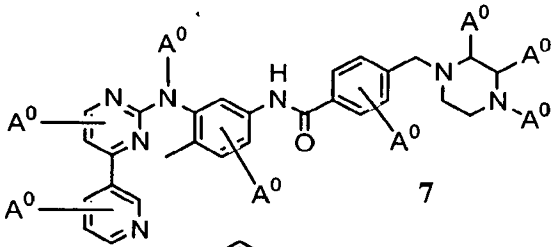
Aº
N
H
H
N
N
N
N
N
O
N

5



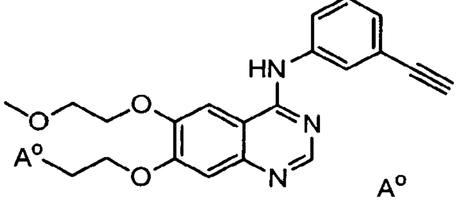
Aº
N
H
H
N
N
N
N
O
N

6

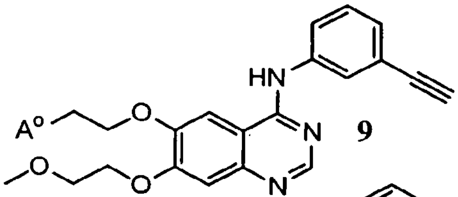


A0
A0
H
A0
N
N
N
N
A0
N
A0
O
A0
N
A0
A0
N

7



8



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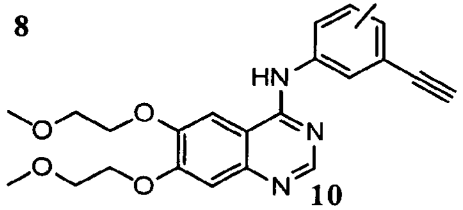

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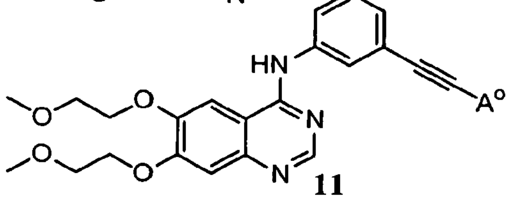

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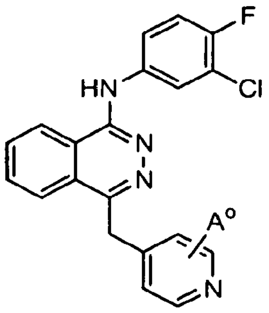

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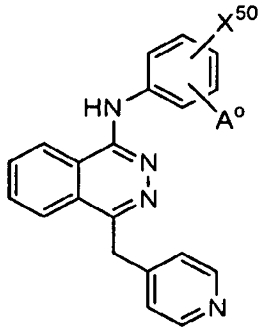

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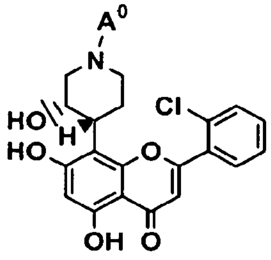
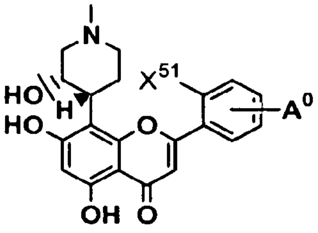
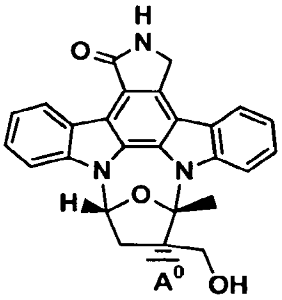

A0
N
HO
H
Cl
HO
O
OH
O

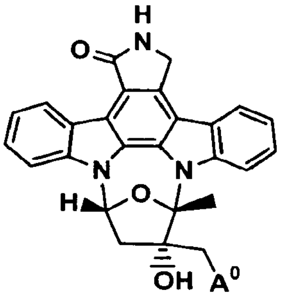
14


N
X51
HO
H
HO
O
A0
OH
O

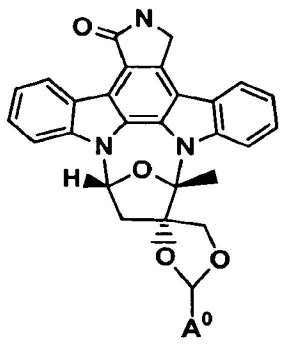
15


H
O
N
N
N
H
O
A0
OH

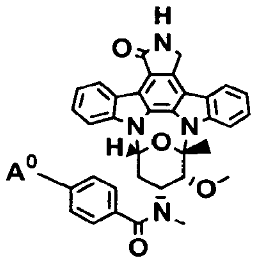
16


H
O
N
N
N
H
O
OH
A0

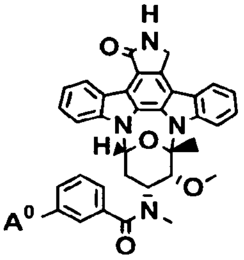
17


H
O
N
N
N
H
O
O
O
A0

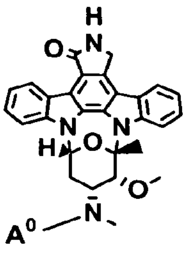
18


H
O
N
N
N
H
O
O
A0
N
O

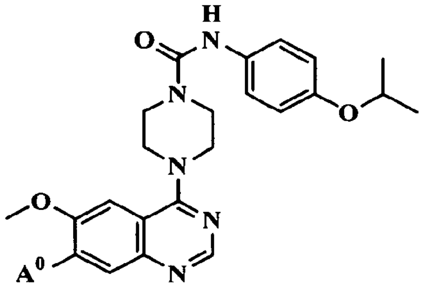
19


H
O
N
N
N
H
O
O
A0
N
O

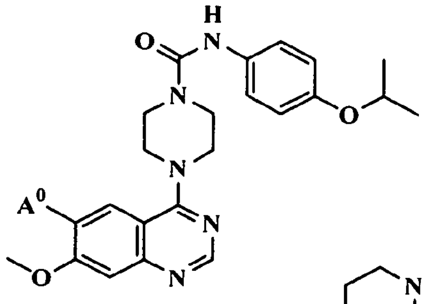
20


H
O
N
N
N
H
O
O
N
A0

21


H
O
N
N
O
N
O
N
A0
N

22



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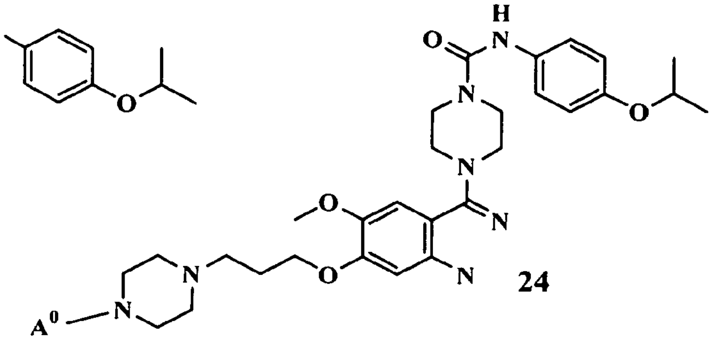

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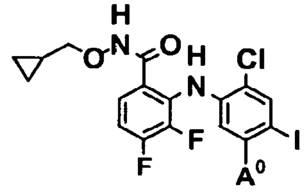

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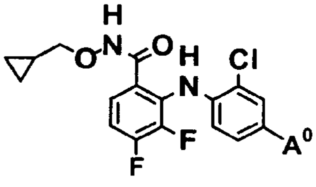

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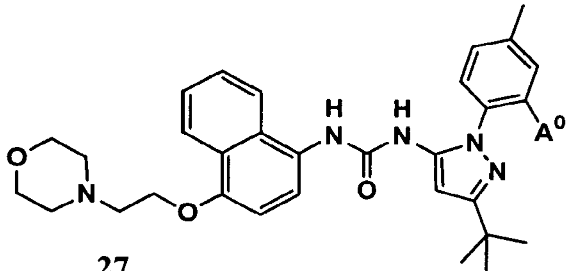

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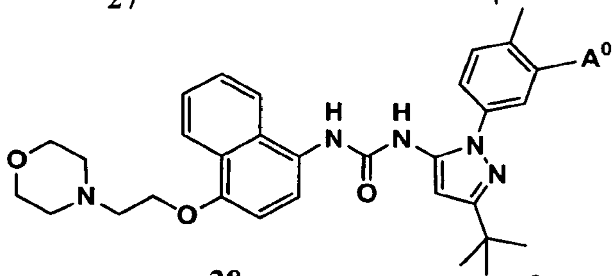

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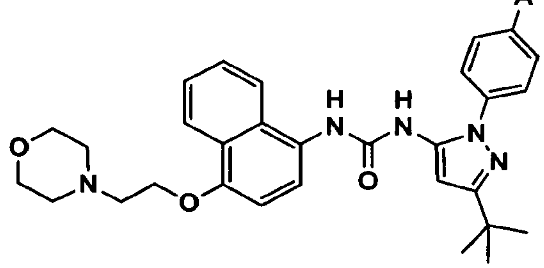

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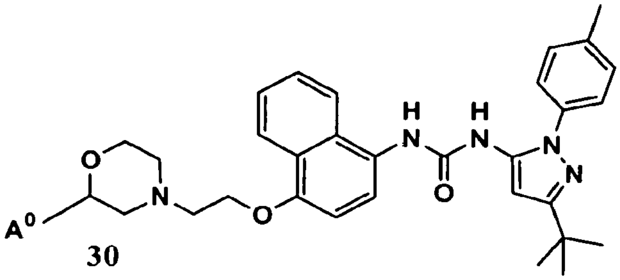

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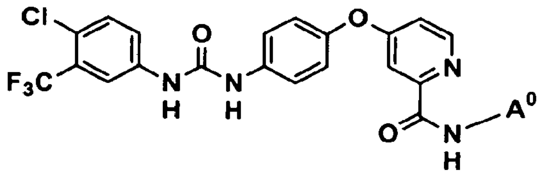
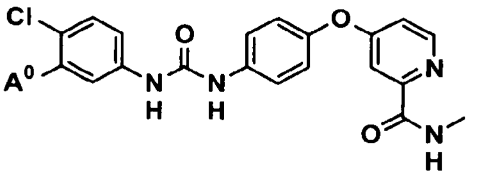


31



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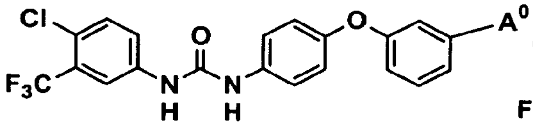

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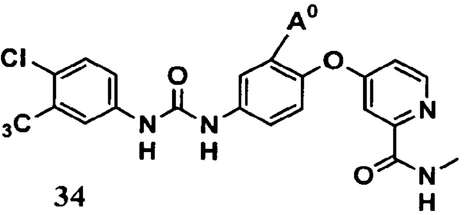
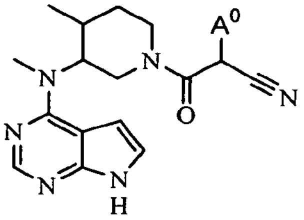
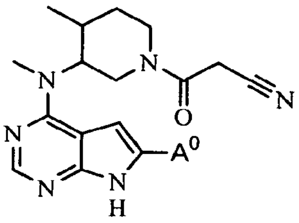


34



35

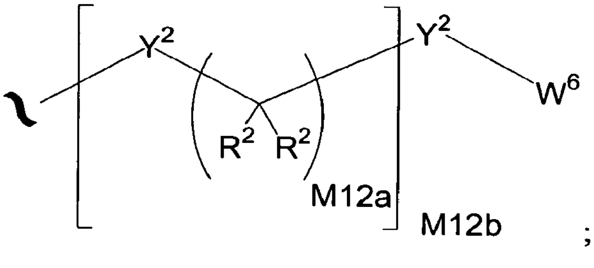


36

wherein:

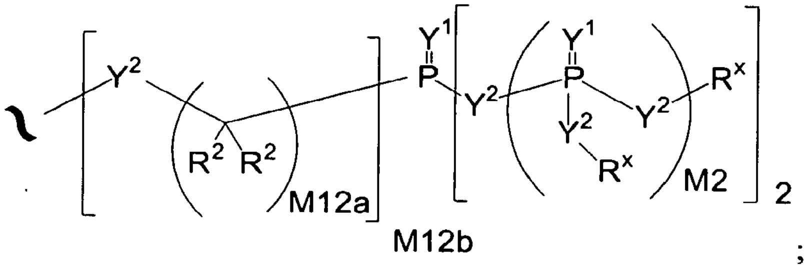
A^0 is A^1;

A^1 is:


Y²
R²
R²
M12a
Y²
W⁶
M12b

;

A^3 is:



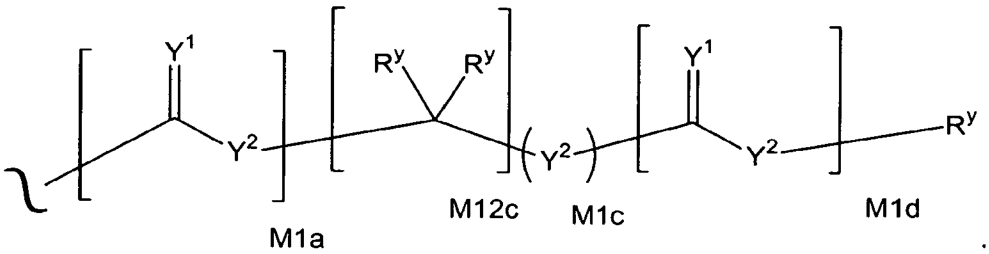
Y2
R2 R2
M12a
M12b
Y1
P
Y2
Y1
P
Y2
Y2
Rx
Rx
M2
2

;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$; and when Y^2 joins two phosphorous atoms Y^2 can also be $C(R^2)(R^2)$;

R^x is independently H, R^2, W^3, a protecting group, or the formula:



Y1
Y2
M1a
Ry
Ry
M12c
Y2
M1c
Y1
Y2
Ry
M1d

;

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, -

$SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

X^{50} is H F, or Cl; and

X^{51} is H or Cl.

The invention provides a pharmaceutical composition comprising an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier.

This invention provides a method of increasing cellular accumulation and retention of drug compounds, thus improving their therapeutic and diagnostic value, comprising linking the compound to one or more (*e.g.*, 1, 2, 3, or 4) phosphonate groups.

The invention also provides a method of inhibiting a kinase, comprising administering to a mammal an amount of a compound of the invention.

The invention also provides a compound of the invention for use in medical therapy (preferably for use in treating a condition associated with kinase activity), as well as the use of a compound of the invention for the manufacture of a medicament useful for the treatment of a condition associated with kinase activity.

The invention also provides processes and novel intermediates disclosed herein which are useful for preparing compounds of the invention. Some of the compounds of the invention are useful to prepare other compounds of the invention.

In another aspect of the invention, the activity of a kinase is inhibited by a method comprising the step of treating a sample suspected of containing a kinase with a compound or composition of the invention.

DETAILED DESCRIPTION OF EXEMPLARY CLAIMS

Reference will now be made in detail to certain claims of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated claims, it will be understood that they are not intended to limit the invention to those claims. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present invention as defined by the claims.

DEFINITIONS

Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

When tradenames are used herein, applicants intend to independently include the tradename product and the active pharmaceutical ingredient(s) of the tradename product.

“Bioavailability” is the degree to which the pharmaceutically active agent becomes available to the target tissue after the agent's introduction into the body. Enhancement of the bioavailability of a pharmaceutically active agent can provide a more efficient and effective treatment for patients because, for a given dose, more of the pharmaceutically active agent will be available at the targeted tissue sites.

The terms "phosphonate" and "phosphonate group" include functional groups or moieties within a molecule that comprises a phosphorous that is 1) single-bonded to a carbon, 2) double-bonded to a heteroatom , 3) single-bonded to a heteroatom, and 4) single-bonded to another heteroatom, wherein each heteroatom can be the same or different. The terms "phosphonate" and "phosphonate group" also include functional groups or moieties that comprise a phosphorous in the same oxidation state as the phosphorous described above, as well as functional groups or moieties that comprise a prodrug moiety that can separate from a compound so that the compound retains a phosphorous having the characteriatics described above. For example, the terms "phosphonate" and "phosphonate group" include phosphonic acid, phosphonic monoester, phosphonic diester, phosphonamidate, and phosphonthioate functional groups. In one specific embodiment of the invention, the terms "phosphonate" and "phosphonate group" include functional groups or moieties within a molecule that comprises a phosphorous that is 1) single-bonded to a carbon, 2) double-bonded to an oxygen, 3) single-bonded to an oxygen, and 4) single-bonded to another oxygen, as well as functional groups or moieties that comprise a prodrug moiety that can separate from a compound so that the compound retains a phosphorous having such characteriatics. In another specific embodiment of the invention, the terms "phosphonate" and "phosphonate group" include functional groups or moieties within a molecule that comprises a phosphorous that is 1) single-bonded to a carbon, 2) double-bonded to an oxygen, 3) single-bonded to an oxygen or nitrogen, and 4) single-bonded to another oxygen or nitrogen, as well as functional groups or moieties that comprise a prodrug moiety that can separate from a compound so that the compound retains a phosphorous having such characteriatics.

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the drug substance, *i.e.* active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically-active compound.

"Prodrug moiety" refers to a labile functional group that separates from the active inhibitory compound during metabolism, systemically, inside a cell, by hydrolysis, enzymatic cleavage, or by some other process (Bundgaard, Hans, "Design and Application of Prodrugs" in A Textbook of Drug Design and Development (1991), P. Krogsgaard-Larsen and H. Bundgaard, Eds. Harwood Academic Publishers, pp. 113-191). Enzymes that are capable of an enzymatic activation mechanism with the phosphonate prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphases. Prodrug moieties can serve to enhance solubility, absorption and lipophilicity to optimize drug delivery, bioavailability and efficacy. A prodrug moiety may include an active metabolite or drug itself.

Exemplary prodrug moieties include the hydrolytically sensitive or labile acyloxymethyl esters $-CH_2OC(=O)R^9$ and acyloxymethyl carbonates $-CH_2OC(=O)OR^9$ where R^9 is C_1-C_6 alkyl, C_1-C_6 substituted alkyl, C_6-C_{20} aryl or C_6-C_{20} substituted aryl. The acyloxyalkyl ester was first used as a prodrug strategy for carboxylic acids and then applied to phosphates and phosphonates by Farquhar *et al.* (1983) *J. Pharm. Sci.* 72: 324; also U.S. Patent Nos. 4816570, 4968788, 5663159 and 5792756. Subsequently, the acyloxyalkyl ester was used to deliver phosphonic acids across cell membranes and to enhance oral bioavailability. A close variant of the acyloxyalkyl ester, the alkoxycarbonyloxyalkyl ester (carbonate), may also enhance oral bioavailability as a prodrug moiety in the compounds of the combinations of the invention. An exemplary acyloxymethyl ester is pivaloyloxymethoxy, (POM) $-CH_2OC(=O)C(CH_3)_3$. An exemplary acyloxymethyl carbonate prodrug moiety is pivaloyloxymethylcarbonate (POC) $-CH_2OC(=O)OC(CH_3)_3$.

The phosphonate group may be a phosphonate prodrug moiety. The prodrug moiety may be sensitive to hydrolysis, such as, but not limited to a pivaloyloxymethyl carbonate (POC) or POM group. Alternatively, the prodrug moiety may be sensitive to enzymatic potentiated cleavage, such as a lactate ester or a phosphonamidate-ester group.

Aryl esters of phosphorus groups, especially phenyl esters, are reported to enhance oral bioavailability (De Lombaert *et al.* (1994) *J. Med. Chem.* 37: 498). Phenyl esters containing a carboxylic ester ortho to the phosphate have also been described (Khamnei and Torrence, (1996) *J. Med. Chem.* 39:4109-4115). Benzyl esters are reported to generate the parent phosphonic acid. In some cases, substituents at the *ortho*-or *para*-position may accelerate the hydrolysis. Benzyl analogs with an acylated phenol or an alkylated phenol may generate the phenolic compound through the action of enzymes, *e.g.*, esterases, oxidases, *etc.*, which in turn undergoes cleavage at the benzylic C–O bond to generate the phosphoric acid and the quinone methide intermediate. Examples of this class of prodrugs are described by Mitchell *et al.* (1992) *J. Chem. Soc. Perkin Trans. II* 2345; Glazier WO 91/19721. Still other benzylic prodrugs have been described containing a carboxylic ester-containing group attached to the benzylic methylene (Glazier WO 91/19721). Thio-containing prodrugs are reported to be useful for the intracellular delivery of phosphonate drugs. These proesters contain an ethylthio group in which the thiol group is either esterified with an acyl group or combined with another thiol group to form a disulfide. Deesterification or reduction of the disulfide generates the free thio intermediate which subsequently breaks down to the phosphoric acid and episulfide (Puech *et al.* (1993) *Antiviral Res.*, 22: 155-174; Benzaria *et al.* (1996) *J. Med. Chem.* 39: 4958). Cyclic phosphonate esters have also been described as prodrugs of phosphorus-containing compounds (Erion *et al.*, US Patent No. 6312662).

"Protecting group" refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. Chemical protecting groups and strategies for protection/deprotection are well known in the art. *See e.g.*, Protective Groups in Organic Chemistry, Theodora W. Greene, John Wiley & Sons, Inc., New York, 1991. Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, *e.g.*, making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

Protected compounds may also exhibit altered, and in some cases, optimized properties *in vitro* and *in vivo*, such as passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds with intended therapeutic effects may be referred to as prodrugs. Another function of a protecting group is to convert the parental drug into a prodrug, whereby the parental drug is released upon conversion of the prodrug *in vivo*. Because active prodrugs may be absorbed more effectively than the parental drug, prodrugs may possess greater potency *in vivo* than the parental drug. Protecting groups are removed either *in vitro,* in the instance of chemical intermediates, or *in vivo*, in the case of prodrugs. With chemical intermediates, it is not particularly important that the resulting products after deprotection, *e.g.*, alcohols, be physiologically acceptable, although in general it is more desirable if the products are pharmacologically innocuous.

Any reference to any of the compounds of the invention also includes a reference to a physiologically acceptable salt thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and NX_4^+ (wherein X is C_1–C_4 alkyl). Physiologically acceptable salts of an hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, benzoic, lactic, fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound of an hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NX_4^+ (wherein X is independently selected from H or a C_1–C_4 alkyl group).

For therapeutic use, salts of active ingredients of the compounds of the invention will be physiologically acceptable, *i.e.* they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived form a physiologically acceptable acid or base, are within the scope of the present invention.

"Alkyl" is C_1-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. Examples are methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$.

"Alkenyl" is C_2-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, sp^2 double bond. Examples include, but are not limited to, ethylene or vinyl ($-CH=CH_2$), allyl ($-CH_2CH=CH_2$), cyclopentenyl ($-C_5H_7$), and 5-hexenyl ($-CH_2CH_2CH_2CH_2CH=CH_2$).

"Alkynyl" is C_2-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, *sp* triple bond. Examples include, but are not limited to, acetylenic ($-C{\equiv}CH$) and propargyl ($-CH_2C{\equiv}CH$).

"Alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical of 1-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. Typical alkylene radicals include, but are not limited to, methylene ($-CH_2-$) 1,2-ethyl ($-CH_2CH_2-$), 1,3-propyl ($-CH_2CH_2CH_2-$), 1,4-butyl ($-CH_2CH_2CH_2CH_2-$), and the like.

"Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. Typical alkenylene radicals include, but are not limited to, 1,2-ethylene ($-CH{=}CH-$).

"Alkynylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. Typical alkynylene radicals include, but are not limited to, acetylene ($-C{\equiv}C-$), propargyl ($-CH_2C{\equiv}C-$), and 4-pentynyl ($-CH_2CH_2CH_2C{\equiv}CH-$).

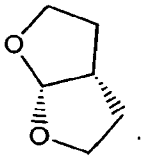
"Aryl" means a monovalent aromatic hydrocarbon radical of 6-20 carbon atoms derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to, radicals derived from benzene, substituted benzene, naphthalene, anthracene, biphenyl, and the like.

"Arylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, , naphthylmethyl, 2-naphthylethan-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group comprises 6 to 20 carbon atoms, *e.g.*, the alkyl moiety, including alkanyl, alkenyl or alkynyl groups, of the arylalkyl group is 1 to 6 carbon atoms and the aryl moiety is 5 to 14 carbon atoms.

"Substituted alkyl", "substituted aryl", and "substituted arylalkyl" mean alkyl, aryl, and arylalkyl respectively, in which one or more hydrogen atoms are each independently replaced with a non-hydrogen substituent. Typical substituents include, but are not limited to, -X, -R, $-O^-$, -OR, -SR, $-S^-$, $-NR_2$, $-NR_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, NC(=O)R, -C(=O)R, -C(=O)NRR $-S(=O)_2O^-$, $-S(=O)_2OH$, $-S(=O)_2R$, -$OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)O_2RR$, $-P(=O)O_2RR$ $-P(=O)(O^-)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)X, -C(S)R, -C(O)OR, $-C(O)O^-$, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, -C(NR)NRR, where each X is independently a halogen: F, Cl, Br, or I; and each R is independently -H, alkyl, aryl, heterocycle, protecting group or prodrug moiety. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted.

"Heterocycle" as used herein includes, by way of example and not limitation, those heterocycles described in Paquette, Leo A.; Principles of Modern Heterocyclic Chemistry (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566. In one specific embodiment of the invention "heterocycle" includes a "carbocycle" as defined herein, wherein one or more (*e.g.*, 1, 2, 3, or 4) carbon atoms have been replaced with a heteroatom (*e.g.*, O, N, or S).

Examples of heterocycles include, by way of example and not limitation, pyridyl, dihydroypyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazoly, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, isatinoyl, and bis-tetrahydrofuranyl:



By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

"Carbocycle" refers to a saturated, unsaturated or aromatic ring having 3 to 7 carbon atoms as a monocycle, 7 to 12 carbon atoms as a bicycle, and up to about 20 carbon atoms as a polycycle. Monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, *e.g.*, arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. Examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl, spiryl and naphthyl.

"Linker" or "link" refers to a chemical moiety comprising a covalent bond or a chain or group of atoms that covalently attaches a phosphonate group to a drug. Linkers include portions of substituents A^1 and A^3, which include moieties such as: repeating units of alkyloxy (*e.g.*, polyethylenoxy, PEG, polymethyleneoxy) and alkylamino (*e.g.*, polyethyleneamino, Jeffamine™); and diacid ester and amides including succinate, succinamide, diglycolate, malonate, and caproamide.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, *e.g.*, melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

The term "treatment" or "treating," to the extent it relates to a disease or condition includes preventing the disease or condition from occurring, inhibiting the disease or condition, eliminating the disease or condition, and/or relieving one or more symptoms of the disease or condition.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

Protecting Groups

In the context of the present invention, protecting groups include prodrug moieties and chemical protecting groups.

Protecting groups are available, commonly known and used, and are optionally used to prevent side reactions with the protected group during synthetic procedures, *i.e.* routes or methods to prepare the compounds of the invention. For the most part the decision as to which groups to protect, when to do so, and the nature of the chemical protecting group "PG" will be dependent upon the chemistry of the reaction to be protected against (*e.g.*, acidic, basic, oxidative, reductive or other conditions) and the intended direction of the synthesis. The PG groups do not need to be, and generally are not, the same if the compound is substituted with multiple PG. In general, PG will be used to protect functional groups such as carboxyl, hydroxyl, thio, or amino groups and to thus prevent side reactions or to otherwise facilitate the synthetic efficiency. The order of deprotection to yield free, deprotected groups is dependent upon the intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order as determined by the artisan.

Various functional groups of the compounds of the invention may be protected. For example, protecting groups for -OH groups (whether hydroxyl, carboxylic acid, phosphonic acid, or other functions) include "ether- or ester-forming groups". Ether- or ester-forming groups are capable of functioning as chemical protecting groups in the synthetic schemes set forth herein. However, some hydroxyl and thio protecting groups are neither ether- nor ester-forming groups, as will be understood by those skilled in the art, and are included with amides, discussed below.

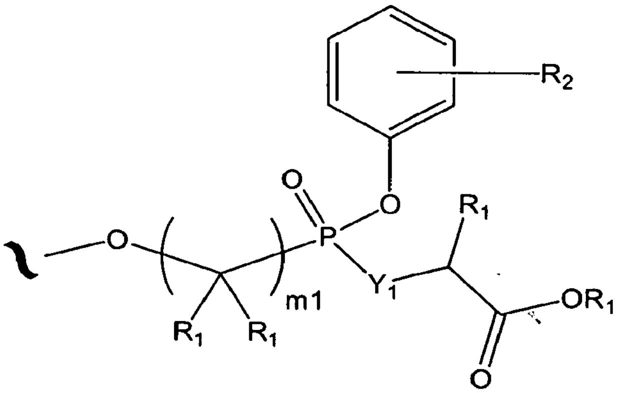
A very large number of hydroxyl protecting groups and amide-forming groups and corresponding chemical cleavage reactions are described in Protective Groups in Organic Synthesis, Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991, ISBN 0-471-62301-6) ("Greene"). See also Kocienski, Philip J.; Protecting Groups (Georg Thieme Verlag Stuttgart, New York, 1994), which is incorporated by reference in its entirety herein. In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-184. For protecting groups for carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for acids see Greene as set forth below. Such groups include by way of example and not limitation, esters, amides, hydrazides, and the like.

Ether- and Ester-forming protecting groups

Ester-forming groups include: (1) phosphonate ester-forming groups, such as phosphonamidate esters, phosphorothioate esters, phosphonate esters, and phosphon-bis-amidates; (2) carboxyl ester-forming groups, and (3) sulphur ester-forming groups, such as sulphonate, sulfate, and sulfinate.

The phosphonate moieties of the compounds of the invention may or may not be prodrug moieties, *i.e.* they may or may be susceptible to hydrolytic or enzymatic cleavage or modification. Certain phosphonate moieties are stable under most or nearly all metabolic conditions. For example, a dialkylphosphonate, where the alkyl groups are two or more carbons, may have appreciable stability *in vivo* due to a slow rate of hydrolysis.

Within the context of phosphonate prodrug moieties, a large number of structurally-diverse prodrugs have been described for phosphonic acids (Freeman and Ross in Progress in Medicinal Chemistry 34: 112-147 (1997) and are included within the scope of the present invention. An exemplary phosphonate ester-forming group is the phenyl carbocycle in substructure A_3 having the formula:



wherein R_1 may be H or C_1–C_{12} alkyl; m1 is 1, 2, 3, 4, 5, 6, 7 or 8, and the phenyl carbocycle is substituted with 0 to 3 R_2 groups. Where Y_1 is O, a lactate ester is formed, and where Y_1 is $N(R_2)$, $N(OR_2)$ or $N(N(R_2)_2$, a phosphonamidate ester results.

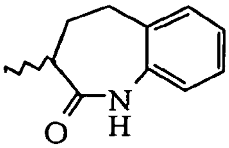
In its ester-forming role, a protecting group typically is bound to any acidic group such as, by way of example and not limitation, a $-CO_2H$ or $-C(S)OH$ group, thereby resulting in $-CO_2R^x$ where R^x is defined herein. Also, R^x for example includes the enumerated ester groups of WO 95/07920.

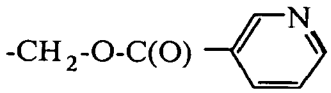
Examples of protecting groups include:

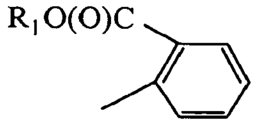
C_3-C_{12} heterocycle (described above) or aryl. These aromatic groups optionally are polycyclic or monocyclic. Examples include phenyl, spiryl, 2- and 3-pyrrolyl, 2- and 3-thienyl, 2- and 4-imidazolyl, 2-, 4- and 5-oxazolyl, 3- and 4-isoxazolyl, 2-, 4- and 5-thiazolyl, 3-, 4- and 5-isothiazolyl, 3- and 4-pyrazolyl, 1-, 2-, 3- and 4-pyridinyl, and 1-, 2-, 4- and 5-pyrimidinyl,

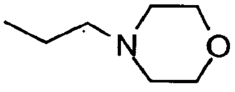
C_3-C_{12} heterocycle or aryl substituted with halo, R^1, R^1-O-C_1-C_{12} alkylene, C_1-C_{12} alkoxy, CN, NO_2, OH, carboxy, carboxyester, thiol, thioester, C_1-C_{12} haloalkyl (1-6 halogen atoms), C_2-C_{12} alkenyl or C_2-C_{12} alkynyl. Such groups include 2-, 3- and 4-alkoxyphenyl (C_1-C_{12} alkyl), 2-, 3- and 4-methoxyphenyl, 2-, 3- and 4-ethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-diethoxyphenyl, 2- and 3-carboethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-5-hydroxyphenyl, 2- and 3-ethoxy-6-hydroxyphenyl, 2-, 3- and 4-O-acetylphenyl, 2-, 3- and 4-dimethylaminophenyl, 2-, 3- and 4-methylmercaptophenyl, 2-, 3- and 4-halophenyl (including 2-, 3- and 4-fluorophenyl and 2-, 3- and 4-chlorophenyl), 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-biscarboxyethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dihalophenyl (including 2,4-difluorophenyl and 3,5-difluorophenyl), 2-, 3- and 4-haloalkylphenyl (1 to 5 halogen atoms, C_1-C_{12} alkyl including 4-trifluoromethylphenyl), 2-, 3- and 4-cyanophenyl, 2-, 3- and 4-nitrophenyl, 2-, 3- and 4-haloalkylbenzyl (1 to 5 halogen atoms, C_1-C_{12} alkyl including 4-trifluoromethylbenzyl and 2-, 3- and 4-trichloromethylphenyl and 2-, 3- and 4-trichloromethylphenyl), 4-N-methylpiperidinyl, 3-N-methylpiperidinyl, 1-ethylpiperazinyl, benzyl, alkylsalicylphenyl (C_1-C_4 alkyl, including 2-, 3- and 4-ethylsalicylphenyl), 2-,3- and 4-acetylphenyl, 1,8-dihydroxynaphthyl ($-C_{10}H_6-OH$) and aryloxy ethyl [C_6-C_9 aryl (including phenoxy ethyl)], 2,2'-

dihydroxybiphenyl, 2-, 3- and 4-N,N-dialkylaminophenol, $-C_6H_4CH_2-N(CH_3)_2$, trimethoxybenzyl, triethoxybenzyl, 2-alkyl pyridinyl (C_{1-4} alkyl);



; 

; 

; C_4 - C_8 esters of 2-carboxyphenyl; and C_1-C_4 alkylene-C_3-C_6 aryl (including benzyl, $-CH_2$-pyrrolyl, $-CH_2$-thienyl, $-CH_2$-imidazolyl, $-CH_2$-oxazolyl, $-CH_2$-isoxazolyl, $-CH_2$-thiazolyl, $-CH_2$-isothiazolyl, $-CH_2$-pyrazolyl, $-CH_2$-pyridinyl and $-CH_2$-pyrimidinyl) substituted in the aryl moiety by 3 to 5 halogen atoms or 1 to 2 atoms or groups selected from halogen, C_1-C_{12} alkoxy (including methoxy and ethoxy), cyano, nitro, OH, C_1-C_{12} haloalkyl (1 to 6 halogen atoms; including $-CH_2CCl_3$), C_1-C_{12} alkyl (including methyl and ethyl), C_2-C_{12} alkenyl or C_2-C_{12} alkynyl; alkoxy ethyl [C_1-C_6 alkyl including $-CH_2-CH_2-O-CH_3$ (methoxy ethyl)]; alkyl substituted by any of the groups set forth above for aryl, in particular OH or by 1 to 3 halo atoms (including $-CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$, $-(CH_2)_4CH_3$, $-(CH_2)_5CH_3$, $-CH_2CH_2F$, $-CH_2CH_2Cl$, $-CH_2CF_3$, and $-CH_2CCl_3$); 

; -N-2-propylmorpholino, 2,3-dihydro-6-hydroxyindene, sesamol, catechol monoester, $-CH_2-C(O)-N(R^1)_2$, $-CH_2-S(O)(R^1)$, $-CH_2-S(O)_2(R^1)$, $-CH_2-CH(OC(O)CH_2R^1)-CH_2(OC(O)CH_2R^1)$, cholesteryl, enolpyruvate ($HOOC-C(=CH_2)-$), glycerol;

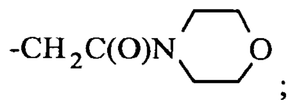
a 5 or 6 carbon monosaccharide, disaccharide or oligosaccharide (3 to 9 monosaccharide residues);

triglycerides such as α-D-β-diglycerides (wherein the fatty acids composing glyceride lipids generally are naturally occurring saturated or unsaturated C_{6-26}, C_{6-18} or C_{6-10} fatty acids such as linoleic, lauric, myristic, palmitic, stearic, oleic, palmitoleic, linolenic and the like fatty acids) linked to acyl of the parental compounds herein through a glyceryl oxygen of the triglyceride;

phospholipids linked to the carboxyl group through the phosphate of the phospholipid;

phthalidyl (shown in Fig. 1 of Clayton *et al.*, *Antimicrob. Agents Chemo.* (1974) 5(6):670-671;

cyclic carbonates such as (5-R_d-2-oxo-1,3-dioxolen-4-yl) methyl esters (Sakamoto *et al.*, *Chem. Pharm. Bull.* (1984) 32(6)2241-2248) where R_d is R_1, R_4 or aryl; and



;

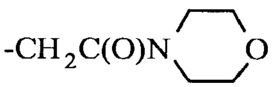
The hydroxyl groups of the compounds of this invention optionally are substituted with one of groups III, IV or V disclosed in WO 94/21604, or with isopropyl.

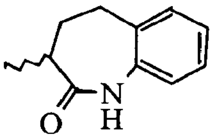
Table A lists examples of protecting group ester moieties that for example can be bonded via oxygen to -C(O)O- and -P(O)(O-)$_2$ groups. Several amidates also are shown, which are bound directly to -C(O)- or -P(O)$_2$. Esters of structures 1-5, 8-10 and 16, 17, 19-22 are synthesized by reacting the compound herein having a free hydroxyl with the corresponding halide (chloride or acyl chloride and the like) and N ,N-dicyclohexyl-N-morpholine carboxamidine (or another base such as DBU, triethylamine, $CsCO_3$, N,N-dimethylaniline and the like) in DMF (or other solvent such as acetonitrile or N-methylpyrrolidone). When the compound to be protected is a phosphonate, the esters of structures 5-7, 11, 12, 21, and 23-26 are synthesized by reaction of the alcohol or alkoxide salt (or the corresponding amines in the case of compounds such as 13, 14 and 15) with the monochlorophosphonate or dichlorophosphonate (or another activated phosphonate).

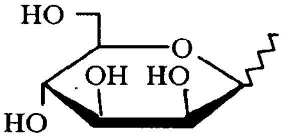
TABLE A

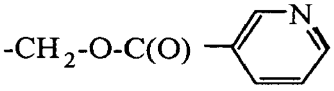
1. $-CH_2-C(O)-N(R_1)_2$ *	10. $-CH_2-O-C(O)-C(CH_3)_3$
2. $-CH_2-S(O)(R_1)$	11. $-CH_2-CCl_3$
3. $-CH_2-S(O)_2(R_1)$	12. $-C_6H_5$

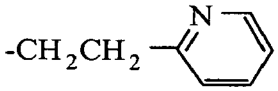
4. $-CH_2-O-C(O)-CH_2-C_6H_5$
5. 3-cholesteryl
6. 3-pyridyl
7. N-ethylmorpholino
8. $-CH_2-O-C(O)-C_6H_5$
9. $-CH_2-O-C(O)-CH_2CH_3$
13. $-NH-CH_2-C(O)O-CH_2CH_3$
14. $-N(CH_3)-CH_2-C(O)O-CH_2CH_3$
15. $-NHR_1$
16. $-CH_2-O-C(O)-C_{10}H_{15}$
17. $-CH_2-O-C(O)-CH(CH_3)_2$
18. $-CH_2-C\#H(OC(O)CH_2R_1)-CH_2-$ $-(OC(O)CH_2R_1)*$

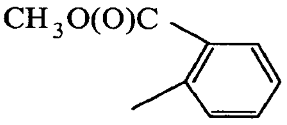
19.


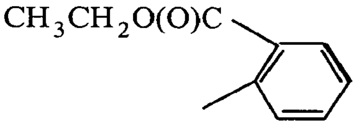
20.


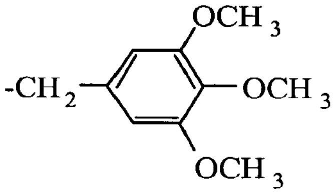
21.


22.


23.


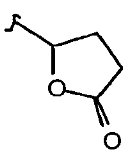
24.


25.


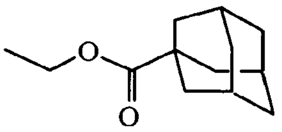
26.

OCH3
-CH2
OCH3
OCH3

# - chiral center is (R), (S) or racemate.

Other esters that are suitable for use herein are described in EP 632048.

Protecting groups also includes "double ester" forming profunctionalities such as $-CH_2OC(O)OCH_3$,  $-CH_2SCOCH_3$, $-CH_2OCON(CH_3)_2$, or alkyl- or aryl-acyloxyalkyl groups of the structure $-CH(R^1 \text{ or } W^5)O((CO)R^{37})$ or

-CH(R^1 or W^5)((CO)OR^{38}) (linked to oxygen of the acidic group) wherein R^{37} and R^{38} are alkyl, aryl, or alkylaryl groups (see U.S. Patent No. 4968788). Frequently R^{37} and R^{38} are bulky groups such as branched alkyl, ortho-substituted aryl, meta-substituted aryl, or combinations thereof, including normal, secondary, iso- and tertiary alkyls of 1-6 carbon atoms. An example is the pivaloyloxymethyl group. These are of particular use with prodrugs for oral administration. Examples of such useful protecting groups are alkylacyloxymethyl esters and their derivatives, including -$CH(CH_2CH_2OCH_3)OC(O)C(CH_3)_3$,



; -$CH_2OC(O)C_{10}H_{15}$, -$CH_2OC(O)C(CH_3)_3$, -$CH(CH_2OCH_3)OC(O)C(CH_3)_3$, -$CH(CH(CH_3)_2)OC(O)C(CH_3)_3$, -$CH_2OC(O)CH_2CH(CH_3)_2$, -$CH_2OC(O)C_6H_{11}$, -$CH_2OC(O)C_6H_5$, -$CH_2OC(O)C_{10}H_{15}$, -$CH_2OC(O)CH_2CH_3$, -$CH_2OC(O)CH(CH_3)_2$, -$CH_2OC(O)C(CH_3)_3$ and -$CH_2OC(O)CH_2C_6H_5$.

In some claims the protected acidic group is an ester of the acidic group and is the residue of a hydroxyl-containing functionality. In other claims, an amino compound is used to protect the acid functionality. The residues of suitable hydroxyl or amino-containing functionalities are set forth above or are found in WO 95/07920. Of particular interest are the residues of amino acids, amino acid esters, polypeptides, or aryl alcohols. Typical amino acid, polypeptide and carboxyl-esterified amino acid residues are described on pages 11-18 and related text of WO 95/07920 as groups L1 or L2. WO 95/07920 expressly teaches the amidates of phosphonic acids, but it will be understood that such amidates are formed with any of the acid groups set forth herein and the amino acid residues set forth in WO 95/07920.

Typical esters for protecting acidic functionalities are also described in WO 95/07920, again understanding that the same esters can be formed with the acidic groups herein as with the phosphonate of the '920 publication. Typical ester groups are defined at least on WO 95/07920 pages 89-93 (under R^{31} or

R^{35}), the table on page 105, and pages 21-23 (as R). Of particular interest are esters of unsubstituted aryl such as phenyl or arylalkyl such benzyl, or hydroxy-, halo-, alkoxy-, carboxy- and/or alkylestercarboxy-substituted aryl or alkylaryl, especially phenyl, ortho-ethoxyphenyl, or C_1-C_4 alkylestercarboxyphenyl (salicylate C_1-C_{12} alkylesters).

The protected acidic groups, particularly when using the esters or amides of WO 95/07920, are useful as prodrugs for oral administration. However, it is not essential that the acidic group be protected in order for the compounds of this invention to be effectively administered by the oral route. When the compounds of the invention having protected groups, in particular amino acid amidates or substituted and unsubstituted aryl esters are administered systemically or orally they are capable of hydrolytic cleavage *in vivo* to yield the free acid.

One or more of the acidic hydroxyls are protected. If more than one acidic hydroxyl is protected then the same or a different protecting group is employed, *e.g.*, the esters may be different or the same, or a mixed amidate and ester may be used.

Typical hydroxy protecting groups described in Greene (pages 14-118) include substituted methyl and alkyl ethers, substituted benzyl ethers, silyl ethers, esters including sulfonic acid esters, and carbonates. For example:

- Ethers (methyl, *t*-butyl, allyl);
- Substituted Methyl Ethers (Methoxymethyl, Methylthiomethyl, *t*-Butylthiomethyl, (Phenyldimethylsilyl)methoxymethyl, Benzyloxymethyl, *p*-Methoxybenzyloxymethyl, (4-Methoxyphenoxy)methyl, Guaiacolmethyl, *t*-Butoxymethyl, 4-Pentenyloxymethyl, Siloxymethyl, 2-Methoxyethoxymethyl, 2,2,2-Trichloroethoxymethyl, Bis(2-chloroethoxy)methyl, 2-(Trimethylsilyl)ethoxymethyl, Tetrahydropyranyl, 3-Bromotetrahydropyranyl, Tetrahydropthiopyranyl, 1-Methoxycyclohexyl, 4-Methoxytetrahydropyranyl, 4-Methoxytetrahydrothiopyranyl, 4-Methoxytetrahydropthiopyranyl *S,S*-Dioxido, 1-[(2-Chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-Dioxan-2-yl, Tetrahydrofuranyl, Tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl));

- Substituted Ethyl Ethers (1-Ethoxyethyl, 1-(2-Chloroethoxy)ethyl, 1-Methyl-1-methoxyethyl, 1-Methyl-1-benzyloxyethyl, 1-Methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-Trichloroethyl, 2-Trimethylsilylethyl, 2-(Phenylselenyl)ethyl,
- *p*-Chlorophenyl, *p*-Methoxyphenyl, 2,4-Dinitrophenyl, Benzyl);
- Substituted Benzyl Ethers (*p*-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *p*-Halobenzyl, 2,6-Dichlorobenzyl, *p*-Cyanobenzyl, *p*-Phenylbenzyl, 2- and 4-Picolyl, 3-Methyl-2-picolyl *N*-Oxido, Diphenylmethyl, *p,p*'-Dinitrobenzhydryl, 5-Dibenzosuberyl, Triphenylmethyl, α-Naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, Di(*p*-methoxyphenyl)phenylmethyl, Tri(*p*-methoxyphenyl)methyl, 4-(4'-Bromophenacyloxy)phenyldiphenylmethyl, 4,4',4”-Tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4”-Tris(levulinoyloxyphenyl)methyl, 4,4',4”-Tris(benzoyloxyphenyl)methyl, 3-(Imidazol-1-ylmethyl)bis(4',4”-dimethoxyphenyl)methyl, 1,1-Bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-Anthryl, 9-(9-Phenyl)xanthenyl, 9-(9-Phenyl-10-oxo)anthryl, 1,3-Benzodithiolan-2-yl, Benzisothiazolyl *S,S*-Dioxido);
- Silyl Ethers (Trimethylsilyl, Triethylsilyl, Triisopropylsilyl, Dimethylisopropylsilyl, Diethylisopropylsilyl, Dimethylthexylsilyl, *t*-Butyldimethylsilyl, *t*-Butyldiphenylsilyl, Tribenzylsilyl, Tri-*p*-xylylsilyl, Triphenylsilyl, Diphenylmethylsilyl, *t*-Butylmethoxyphenylsilyl);
- Esters (Formate, Benzoylformate, Acetate, Choroacetate, Dichloroacetate, Trichloroacetate, Trifluoroacetate, Methoxyacetate, Triphenylmethoxyacetate, Phenoxyacetate, *p*-Chlorophenoxyacetate, *p*-poly-Phenylacetate, 3-Phenylpropionate, 4-Oxopentanoate (Levulinate), 4,4-(Ethylenedithio)pentanoate, Pivaloate, Adamantoate, Crotonate, 4-Methoxycrotonate, Benzoate, *p*-Phenylbenzoate, 2,4,6-Trimethylbenzoate (Mesitoate));
- Carbonates (Methyl, 9-Fluorenylmethyl, Ethyl, 2,2,2-Trichloroethyl, 2-(Trimethylsilyl)ethyl, 2-(Phenylsulfonyl)ethyl, 2-(Triphenylphosphonio)ethyl, Isobutyl, Vinyl, Allyl, *p*-Nitrophenyl, Benzyl,

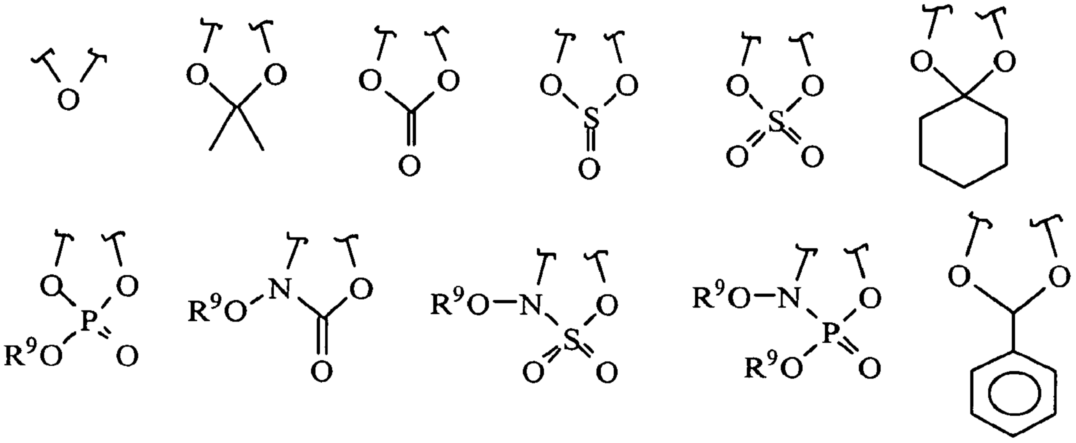
p-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *S*-Benzyl Thiocarbonate, 4-Ethoxy-1-naphthyl, Methyl Dithiocarbonate);

- Groups With Assisted Cleavage (2-Iodobenzoate, 4-Azidobutyrate, 4-Nitro-4-methylpentanoate, *o*-(Dibromomethyl)benzoate, 2-Formylbenzenesulfonate, 2-(Methylthiomethoxy)ethyl Carbonate, 4-(Methylthiomethoxy)butyrate, 2-(Methylthiomethoxymethyl)benzoate); Miscellaneous Esters (2,6-Dichloro-4-methylphenoxyacetate, 2,6-Dichloro-4-(1,1,3,3 tetramethylbutyl)phenoxyacetate, 2,4-Bis(1,1-dimethylpropyl)phenoxyacetate, Chlorodiphenylacetate, Isobutyrate, Monosuccinate, (*E*)-2-Methyl-2-butenoate (Tigloate), *o*-(Methoxycarbonyl)benzoate, *p*-poly-Benzoate, α-Naphthoate, Nitrate, Alkyl *N,N,N',N'*-Tetramethylphosphorodiamidate, *N*-Phenylcarbamate, Borate, Dimethylphosphinothioyl, 2,4-Dinitrophenylsulfenate); and
- Sulfonates (Sulfate, Methanesulfonate (Mesylate), Benzylsulfonate, Tosylate).

Typical 1,2-diol protecting groups (thus, generally where two OH groups are taken together with the protecting functionality) are described in Greene at pages 118-142 and include Cyclic Acetals and Ketals (Methylene, Ethylidene, 1-*t*-Butylethylidene, 1-Phenylethylidene, (4-Methoxyphenyl)ethylidene, 2,2,2-Trichloroethylidene, Acetonide (Isopropylidene), Cyclopentylidene, Cyclohexylidene, Cycloheptylidene, Benzylidene, *p*-Methoxybenzylidene, 2,4-Dimethoxybenzylidene, 3,4-Dimethoxybenzylidene, 2-Nitrobenzylidene); Cyclic Ortho Esters (Methoxymethylene, Ethoxymethylene, Dimethoxymethylene, 1-Methoxyethylidene, 1-Ethoxyethylidine, 1,2-Dimethoxyethylidene, α-Methoxybenzylidene, 1-(*N,N*-Dimethylamino)ethylidene Derivative, α -(*N,N*-Dimethylamino)benzylidene Derivative, 2-Oxacyclopentylidene); Silyl Derivatives (Di-*t*-butylsilylene Group, 1,3-(1,1,3,3-Tetraisopropyldisiloxanylidene), and Tetra-*t*-butoxydisiloxane-1,3-diylidene), Cyclic Carbonates, Cyclic Boronates, Ethyl Boronate and Phenyl Boronate.

More typically, 1,2-diol protecting groups include those shown in Table B, still more typically, epoxides, acetonides, cyclic ketals and aryl acetals.

Table B



wherein R^9 is C_1-C_6 alkyl.

Amino protecting groups

Another set of protecting groups include any of the typical amino protecting groups described by Greene at pages 315-385. They include:

- Carbamates: (methyl and ethyl, 9-fluorenylmethyl, 9(2-sulfo)fluorenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl, 4-methoxyphenacyl);
- Substituted Ethyl: (2,2,2-trichoroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 1,1-dimethyl-2-haloethyl, 1,1-dimethyl-2,2-dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenylyl)ethyl, 1-(3,5-di-*t*-butylphenyl)-1-methylethyl, 2-(2'- and 4'-pyridyl)ethyl, 2-(*N,N*-dicyclohexylcarboxamido)ethyl, *t*-butyl, 1-adamantyl, vinyl, allyl, 1-isopropylallyl, cinnamyl, 4-nitrocinnamyl, 8-quinolyl, *N*-hydroxypiperidinyl, alkyldithio, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, *p*-bromobenzyl, *p*-chlorobenzyl, 2,4-dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, diphenylmethyl);
- Groups With Assisted Cleavage: (2-methylthioethyl, 2-methylsulfonylethyl, 2-(*p*-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl, 4-methylthiophenyl, 2,4-dimethylthiophenyl, 2-phosphonioethyl, 2-triphenylphosphonioisopropyl, 1,1-dimethyl-2-cyanoethyl, *m*-choro-*p*-

acyloxybenzyl, *p*-(dihydroxyboryl)benzyl, 5-benzisoxazolylmethyl, 2-(trifluoromethyl)-6-chromonylmethyl);

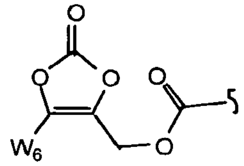
- Groups Capable of Photolytic Cleavage: (*m*-nitrophenyl, 3,5-dimethoxybenzyl, *o*-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, phenyl(*o*-nitrophenyl)methyl); Urea-Type Derivatives (phenothiazinyl-(10)-carbonyl, *N'*-*p*-toluenesulfonylaminocarbonyl, *N'*-phenylaminothiocarbonyl);
- Miscellaneous Carbamates: (*t*-amyl, *S*-benzyl thiocarbamate, *p*-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, *p*-decyloxybenzyl, diisopropylmethyl, 2,2-dimethoxycarbonylvinyl, *o*-(*N,N*-dimethylcarboxamido)benzyl, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propyl, 1,1-dimethylpropynyl, di(2-pyridyl)methyl, 2-furanylmethyl, 2-Iodoethyl, Isobornyl, Isobutyl, Isonicotinyl, *p*-(*p*'-Methoxyphenylazo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-methyl-1-cyclopropylmethyl, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl, 1-methyl-1-(*p*-phenylazophenyl)ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(4-pyridyl)ethyl, phenyl, *p*-(phenylazo)benzyl, 2,4,6-tri-*t*-butylphenyl, 4-(trimethylammonium)benzyl, 2,4,6-trimethylbenzyl);
- Amides: (*N*-formyl, *N*-acetyl, *N*-choroacetyl, *N*-trichoroacetyl, *N*-trifluoroacetyl, *N*-phenylacetyl, *N*-3-phenylpropionyl, *N*-picolinoyl, *N*-3-pyridylcarboxamide, *N*-benzoylphenylalanyl, *N*-benzoyl, *N*-*p*-phenylbenzoyl);
- Amides With Assisted Cleavage: (*N*-*o*-nitrophenylacetyl, *N*-*o*-nitrophenoxyacetyl, *N*-acetoacetyl, (*N'*-dithiobenzyloxycarbonylamino)acetyl, *N*-3-(*p*-hydroxyphenyl)propionyl, *N*-3-(*o*-nitrophenyl)propionyl, *N*-2-methyl-2-(*o*-nitrophenoxy)propionyl, *N*-2-methyl-2-(*o*-phenylazophenoxy)propionyl, *N*-4-chlorobutyryl, *N*-3-methyl-3-nitrobutyryl, *N*-*o*-nitrocinnamoyl, *N*-acetylmethionine, *N*-*o*-nitrobenzoyl, *N*-*o*-(benzoyloxymethyl)benzoyl, 4,5-diphenyl-3-oxazolin-2-one);
- Cyclic Imide Derivatives: (*N*-phthalimide, *N*-dithiasuccinoyl, *N*-2,3-diphenylmaleoyl, *N*-2,5-dimethylpyrrolyl, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct, 5-substituted 1,3-dimethyl-1,3,5-

triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3-5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridonyl);

- *N*-Alkyl and *N*-Aryl Amines: (*N*-methyl, *N*-allyl, *N*-[2-(trimethylsilyl)ethoxy]methyl, *N*-3-acetoxypropyl, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), Quaternary Ammonium Salts, *N*-benzyl, *N*-di(4-methoxyphenyl)methyl, *N*-5-dibenzosuberyl, *N*-triphenylmethyl, *N*-(4-methoxyphenyl)diphenylmethyl, *N*-9-phenylfluorenyl, *N*-2,7-dichloro-9-fluorenylmethylene, *N*-ferrocenylmethyl, *N*-2-picolylamine *N'*-oxide);
- Imine Derivatives: (*N*-1,1-dimethylthiomethylene, *N*-benzylidene, *N*-*p*-methoxybenylidene, *N*-diphenylmethylene, *N*-[(2-pyridyl)mesityl]methylene, *N*,(*N'*,*N'*-dimethylaminomethylene, *N*,*N'*-isopropylidene, *N*-*p*-nitrobenzylidene, *N*-salicylidene, *N*-5-chlorosalicylidene, *N*-(5-chloro-2-hydroxyphenyl)phenylmethylene, *N*-cyclohexylidene);
- Enamine Derivatives: (*N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl));
- *N*-Metal Derivatives (*N*-borane derivatives, *N*-diphenylborinic acid derivatives, *N*-[phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, *N*-copper or *N*-zinc chelate);
- N-N Derivatives: (*N*-nitro, *N*-nitroso, *N*-oxide);
- N-P Derivatives: (*N*-diphenylphosphinyl, *N*-dimethylthiophosphinyl, *N*-diphenylthiophosphinyl, *N*-dialkyl phosphoryl, *N*-dibenzyl phosphoryl, *N*-diphenyl phosphoryl);
- N-Si Derivatives, N-S Derivatives, and N-Sulfenyl Derivatives: (*N*-benzenesulfenyl, *N*-*o*-nitrobenzenesulfenyl, *N*-2,4-dinitrobenzenesulfenyl, *N*-pentachlorobenzenesulfenyl, *N*-2-nitro-4-methoxybenzenesulfenyl, *N*-triphenylmethylsulfenyl, *N*-3-nitropyridinesulfenyl); and *N*-sulfonyl Derivatives (*N*-*p*-toluenesulfonyl, *N*-benzenesulfonyl, *N*-2,3,6-trimethyl-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethoxybenzenesulfonyl, *N*-2,6-dimethyl-4-methoxybenzenesulfonyl, *N*-pentamethylbenzenesulfonyl, *N*-2,3,5,6,-tetramethyl-4-methoxybenzenesulfonyl, *N*-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethylbenzenesulfonyl, *N*-2,6-dimethoxy-4-methylbenzenesulfonyl, *N*-2,2,5,7,8-pentamethylchroman-6-sulfonyl, *N*-methanesulfonyl, *N*-β-trimethylsilyethanesulfonyl, *N*-9-

anthracenesulfonyl, *N*-4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonyl, *N*-benzylsulfonyl, *N*-trifluoromethylsulfonyl, *N*-phenacylsulfonyl).

More typically, protected amino groups include carbamates and amides, still more typically, $-NHC(O)R^1$ or $-N=CR^1N(R^1)_2$. Another protecting group, also useful as a prodrug for amino or $-NH(R^5)$, is:



See for example Alexander, J. *et al.* (1996) *J. Med. Chem.* 39:480-486.

Amino acid and polypeptide protecting group and conjugates

An amino acid or polypeptide protecting group of a compound of the invention has the structure $R^{15}NHCH(R^{16})C(O)$-, where R^{15} is H, an amino acid or polypeptide residue, or R^5, and R^{16} is defined below.

R^{16} is lower alkyl or lower alkyl (C_1-C_6) substituted with amino, carboxyl, amide, carboxyl ester, hydroxyl, C_6-C_7 aryl, guanidinyl, imidazolyl, indolyl, sulfhydryl, sulfoxide, and/or alkylphosphate. R^{10} also is taken together with the amino acid α N to form a proline residue ($R^{10} = -CH_2)_3-$). However, R^{10} is generally the side group of a naturally-occurring amino acid such as H, $-CH_3$, $-CH(CH_3)_2$, $-CH_2-CH(CH_3)_2$, $-CHCH_3-CH_2-CH_3$, $-CH_2-C_6H_5$, $-CH_2CH_2-S-CH_3$, $-CH_2OH$, $-CH(OH)-CH_3$, $-CH_2-SH$, $-CH_2-C_6H_4OH$, $-CH_2-CO-NH_2$, $-CH_2-CH_2-CO-NH_2$, $-CH_2-COOH$, $-CH_2-CH_2-COOH$, $-(CH_2)_4-NH_2$ and $-(CH_2)_3-NH-C(NH_2)-NH_2$. R_{10} also includes 1-guanidinoprop-3-yl, benzyl, 4-hydroxybenzyl, imidazol-4-yl, indol-3-yl, methoxyphenyl and ethoxyphenyl.

Another set of protecting groups include the residue of an amino-containing compound, in particular an amino acid, a polypeptide, a protecting group, $-NHSO_2R$, $NHC(O)R$, $-N(R)_2$, NH_2 or $-NH(R)(H)$, whereby for example a carboxylic acid is reacted, *i.e.* coupled, with the amine to form an amide, as in

$C(O)NR_2$. A phosphonic acid may be reacted with the amine to form a phosphonamidate, as in $-P(O)(OR)(NR_2)$.

In general, amino acids have the structure $R^{17}C(O)CH(R^{16})NH-$, where R^{17} is -OH, -OR, an amino acid or a polypeptide residue. Amino acids are low molecular weight compounds, on the order of less than about 1000 MW and which contain at least one amino or imino group and at least one carboxyl group. Generally the amino acids will be found in nature, *i.e.*, can be detected in biological material such as bacteria or other microbes, plants, animals or man. Suitable amino acids typically are alpha amino acids, *i.e.* compounds characterized by one amino or imino nitrogen atom separated from the carbon atom of one carboxyl group by a single substituted or unsubstituted alpha carbon atom. Of particular interest are hydrophobic residues such as mono-or di-alkyl or aryl amino acids, cycloalkylamino acids and the like. These residues contribute to cell permeability by increasing the partition coefficient of the parental drug. Typically, the residue does not contain a sulfhydryl or guanidino substituent.

Naturally-occurring amino acid residues are those residues found naturally in plants, animals or microbes, especially proteins thereof. Polypeptides most typically will be substantially composed of such naturally-occurring amino acid residues. These amino acids are glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, methionine, glutamic acid, aspartic acid, lysine, hydroxylysine, arginine, histidine, phenylalanine, tyrosine, tryptophan, proline, asparagine, glutamine and hydroxyproline. Additionally, unnatural amino acids, for example, valanine, phenylglycine and homoarginine are also included. Commonly encountered amino acids that are not gene-encoded may also be used in the present invention. All of the amino acids used in the present invention may be either the D- or L- optical isomer. In addition, other peptidomimetics are also useful in the present invention. For a general review, see Spatola, A. F., in Chemistry and Biochemistry of Amino Acids, Peptides and Proteins, B. Weinstein, eds., Marcel Dekker, New York, p. 267 (1983).

When protecting groups are single amino acid residues or polypeptides they optionally are substituted at R^3 of substituents A^1, A^2 or A^3 in a compound of the invention. These conjugates are produced by forming an amide bond between a carboxyl group of the amino acid (or C-terminal amino acid of a polypeptide for example). Similarly, conjugates are formed between R^3 and an amino group of an amino acid or polypeptide. Generally, only one of any site in the parental molecule is amidated with an amino acid as described herein, although it is within the scope of this invention to introduce amino acids at more than one permitted site. Usually, a carboxyl group of R^3 is amidated with an amino acid. In general, the α-amino or α-carboxyl group of the amino acid or the terminal amino or carboxyl group of a polypeptide are bonded to the parental functionalities, *i.e.*, carboxyl or amino groups in the amino acid side chains generally are not used to form the amide bonds with the parental compound (although these groups may need to be protected during synthesis of the conjugates as described further below).

With respect to the carboxyl-containing side chains of amino acids or polypeptides it will be understood that the carboxyl group optionally will be blocked, *e.g.*, by R^1, esterified with R^5 or amidated. Similarly, the amino side chains R^{16} optionally will be blocked with R^1 or substituted with R^5.

Such ester or amide bonds with side chain amino or carboxyl groups, like the esters or amides with the parental molecule, optionally are hydrolyzable *in vivo* or *in vitro* under acidic (pH <3) or basic (pH >10) conditions. Alternatively, they are substantially stable in the gastrointestinal tract of humans but are hydrolyzed enzymatically in blood or in intracellular environments. The esters or amino acid or polypeptide amidates also are useful as intermediates for the preparation of the parental molecule containing free amino or carboxyl groups. The free acid or base of the parental compound, for example, is readily formed from the esters or amino acid or polypeptide conjugates of this invention by conventional hydrolysis procedures.

When an amino acid residue contains one or more chiral centers, any of the D, L, meso, threo or erythro (as appropriate) racemates, scalemates or mixtures thereof may be used. In general, if the intermediates are to be hydrolyzed non-enzymatically (as would be the case where the amides are used as chemical intermediates for the free acids or free amines), D isomers are useful. On the other hand, L isomers are more versatile since they can be susceptible to both non-enzymatic and enzymatic hydrolysis, and are more efficiently transported by amino acid or dipeptidyl transport systems in the gastrointestinal tract.

Examples of suitable amino acids whose residues are represented by R^x or R^y include the following:

Glycine;

Aminopolycarboxylic acids, *e.g.*, aspartic acid, β-hydroxyaspartic acid, glutamic acid, β -hydroxyglutamic acid, β-methylaspartic acid, β-methylglutamic acid, β, β-dimethylaspartic acid, γ-hydroxyglutamic acid, β, γ-dihydroxyglutamic acid, β -phenylglutamic acid, γ-methyleneglutamic acid, 3-aminoadipic acid, 2-aminopimelic acid, 2-aminosuberic acid and 2-aminosebacic acid;

Amino acid amides such as glutamine and asparagine;

Polyamino- or polybasic-monocarboxylic acids such as arginine, lysine, β -aminoalanine, γ -aminobutyrine, ornithine, citruline, homoarginine, homocitrulline, hydroxylysine, allohydroxylsine and diaminobutyric acid;

Other basic amino acid residues such as histidine;

Diaminodicarboxylic acids such as α, α'-diaminosuccinic acid, α, α'-diaminoglutaric acid, α, α'-diaminoadipic acid, α, α'-diaminopimelic acid, α, α'-diamino- β-hydroxypimelic acid, α, α'-diaminosuberic acid, α, α'-diaminoazelaic acid, and α, α'-diaminosebacic acid;

Imino acids such as proline, hydroxyproline, allohydroxyproline, γ-methylproline, pipecolic acid, 5-hydroxypipecolic acid, and azetidine-2-carboxylic acid;

A mono- or di-alkyl (typically C_1-C_8 branched or normal) amino acid such as alanine, valine, leucine, allylglycine, butyrine, norvaline, norleucine, heptyline, α-methylserine, α-amino-α-methyl-γ-hydroxyvaleric acid, α-amino- α-methyl-δ-hydroxyvaleric acid, α-amino- α-methyl-ϵ-hydroxycaproic acid, isovaline, α-methylglutamic acid, α-aminoisobutyric acid, α-aminodiethylacetic acid, α-aminodiisopropylacetic acid, α-aminodi-n-propylacetic acid, αaminodiisobutylacetic acid, α-aminodi-n-butylacetic acid, α-aminoethylisopropylacetic acid, α-amino-n-propylacetic acid, α-aminodiisoamyacetic acid, α-methylaspartic acid, α-methylglutamic acid, 1-aminocyclopropane-1-carboxylic acid, isoleucine, alloisoleucine, *tert*-leucine, β-methyltryptophan and α-amino- β-ethyl-β-phenylpropionic acid;

β-phenylserinyl;

Aliphatic α-amino-β-hydroxy acids such as serine, β-hydroxyleucine, β-hydroxynorleucine, β -hydroxynorvaline, and α-amino-β-hydroxystearic acid;

α-Amino, α-, γ-, δ- or ϵ-hydroxy acids such as homoserine, δ -hydroxynorvaline, γ-hydroxynorvaline and ϵ-hydroxynorleucine residues; canavine and canaline; γ -hydroxyornithine;

2-hexosaminic acids such as D-glucosaminic acid or D-galactosaminic acid;

α-Amino-β-thiols such as penicillamine, β-thiolnorvaline or β-thiolbutyrine;

Other sulfur containing amino acid residues including cysteine; homocystine, β-phenylmethionine, methionine, S-allyl-L-cysteine sulfoxide, 2-thiolhistidine, cystathionine, and thiol ethers of cysteine or homocysteine;

Phenylalanine, tryptophan and ring-substituted α-amino acids such as the phenyl- or cyclohexylamino acids α-aminophenylacetic acid, α-aminocyclohexylacetic acid and α-amino-β-cyclohexylpropionic acid; phenylalanine analogues and derivatives comprising aryl, lower alkyl, hydroxy, guanidino, oxyalkylether, nitro, sulfur or halo-substituted phenyl (*e.g.*, tyrosine, methyltyrosine and o-chloro-, p-chloro-, 3,4-dichloro, *o*-, *m*- or *p*-methyl-, 2,4,6-trimethyl-, 2-ethoxy-5-nitro-, 2-hydroxy-5-nitro- and p-nitro-phenylalanine); furyl-, thienyl-, pyridyl-, pyrimidinyl-, purinyl- or naphthyl-alanines; and tryptophan analogues and derivatives including kynurenine, 3-hydroxykynurenine, 2-hydroxytryptophan and 4-carboxytryptophan;

α-Amino substituted amino acids including sarcosine (N-methylglycine), N-benzylglycine, N-methylalanine, N-benzylalanine, N-methylphenylalanine, N-benzylphenylalanine, N-methylvaline and N-benzylvaline; and

α-Hydroxy and substituted α-hydroxy amino acids including serine, threonine, allothreonine, phosphoserine and phosphothreonine.

Polypeptides are polymers of amino acids in which a carboxyl group of one amino acid monomer is bonded to an amino or imino group of the next amino acid monomer by an amide bond. Polypeptides include dipeptides, low molecular weight polypeptides (about 1500-5000 MW) and proteins. Proteins optionally contain 3, 5, 10, 50, 75, 100 or more residues, and suitably are substantially sequence-homologous with human, animal, plant or microbial proteins. They include enzymes (*e.g.*, hydrogen peroxidase) as well as immunogens such as KLH, or antibodies or proteins of any type against which one wishes to raise an immune response. The nature and identity of the polypeptide may vary widely.

The polypeptide amidates are useful as immunogens in raising antibodies against either the polypeptide (if it is not immunogenic in the animal to which it is administered) or against the epitopes on the remainder of the compound of this invention.

Antibodies capable of binding to the parental non-peptidyl compound are used to separate the parental compound from mixtures, for example in diagnosis or manufacturing of the parental compound. The conjugates of parental compound and polypeptide generally are more immunogenic than the polypeptides in closely homologous animals, and therefore make the polypeptide more immunogenic for facilitating raising antibodies against it. Accordingly, the polypeptide or protein may not need to be immunogenic in an animal typically used to raise antibodies, *e.g.*, rabbit, mouse, horse, or rat, but the final product conjugate should be immunogenic in at least one of such animals. The polypeptide optionally contains a peptidolytic enzyme cleavage site at the peptide bond between the first and second residues adjacent to the acidic heteroatom. Such cleavage sites are flanked by enzymatic recognition structures, *e.g.*, a particular sequence of residues recognized by a peptidolytic enzyme.

Peptidolytic enzymes for cleaving the polypeptide conjugates of this invention are well known, and in particular include carboxypeptidases.

Carboxypeptidases digest polypeptides by removing C-terminal residues, and are specific in many instances for particular C-terminal sequences. Such enzymes and their substrate requirements in general are well known. For example, a dipeptide (having a given pair of residues and a free carboxyl terminus) is covalently bonded through its α-amino group to the phosphorus or carbon atoms of the compounds herein. In claims where W_1 is phosphonate it is expected that this peptide will be cleaved by the appropriate peptidolytic enzyme, leaving the carboxyl of the proximal amino acid residue to autocatalytically cleave the phosphonoamidate bond.

Suitable dipeptidyl groups (designated by their single letter code) are AA, AR, AN, AD, AC, AE, AQ, AG, AH, AI, AL, AK, AM, AF, AP, AS, AT, AW, AY, AV, RA, RR, RN, RD, RC, RE, RQ, RG, RH, RI, RL, RK, RM, RF, RP, RS, RT, RW, RY, RV, NA, NR, NN, ND, NC, NE, NQ, NG, NH, NI, NL, NK, NM, NF, NP, NS, NT, NW, NY, NV, DA, DR, DN, DD, DC, DE, DQ, DG, DH, DI, DL, DK, DM, DF, DP, DS, DT, DW, DY, DV, CA, CR, CN, CD, CC, CE, CQ, CG, CH, CI, CL, CK, CM, CF, CP, CS, CT, CW, CY, CV, EA, ER, EN, ED, EC, EE, EQ, EG, EH, EI, EL, EK, EM, EF, EP, ES, ET, EW, EY, EV, QA, QR, QN, QD, QC, QE, QQ, QG, QH, QI, QL, QK, QM, QF, QP, QS, QT, QW, QY, QV, GA, GR, GN, GD, GC, GE, GQ, GG, GH, GI, GL, GK, GM, GF, GP, GS, GT, GW, GY, GV, HA, HR, HN, HD, HC, HE, HQ, HG, HH, HI, HL, HK, HM, HF, HP, HS, HT, HW, HY, HV, IA, IR, IN, ID, IC, IE, IQ, IG, IH, II, IL, IK, IM, IF, IP, IS, IT, IW, IY, IV, LA, LR, LN, LD, LC, LE, LQ, LG, LH, LI, LL, LK, LM, LF, LP, LS, LT, LW, LY, LV, KA, KR, KN, KD, KC, KE, KQ, KG, KH, KI, KL, KK, KM, KF, KP, KS, KT, KW, KY, KV, MA, MR, MN, MD, MC, ME, MQ, MG, MH, MI, ML, MK, MM, MF, MP, MS, MT, MW, MY, MV, FA, FR, FN, FD, FC, FE, FQ, FG, FH, FI, FL, FK, FM, FF, FP, FS, FT, FW, FY, FV, PA, PR, PN, PD, PC, PE, PQ, PG, PH, PI, PL, PK, PM, PF, PP, PS, PT, PW, PY, PV, SA, SR, SN, SD, SC, SE, SQ, SG, SH, SI, SL, SK, SM, SF, SP, SS, ST, SW, SY, SV, TA, TR, TN, TD, TC, TE, TQ, TG, TH, TI, TL, TK, TM, TF, TP, TS, TT, TW, TY, TV, WA, WR, WN, WD, WC, WE, WQ, WG, WH, WI, WL, WK, WM, WF, WP, WS, WT, WW, WY, WV, YA, YR, YN, YD, YC, YE, YQ, YG, YH, YI, YL, YK, YM, YF, YP, YS, YT, YW, YY, YV, VA, VR, VN, VD, VC, VE, VQ, VG, VH, VI, VL, VK, VM, VF, VP, VS, VT, VW, VY and VV.

Tripeptide residues are also useful as protecting groups. When a phosphonate is to be protected, the sequence -X^4-pro-X^5- (where X^4 is any amino acid residue and X^5 is an amino acid residue, a carboxyl ester of proline, or hydrogen) will be cleaved by luminal carboxypeptidase to yield X^4 with a free carboxyl, which in turn is expected to autocatalytically cleave the phosphonoamidate bond. The carboxy group of X^5 optionally is esterified with benzyl.

Dipeptide or tripeptide species can be selected on the basis of known transport properties and/or susceptibility to peptidases that can affect transport to intestinal mucosal or other cell types. Dipeptides and tripeptides lacking an α-amino group are transport substrates for the peptide transporter found in brush border membrane of intestinal mucosal cells (Bai, J.P.F., (1992) *Pharm Res.* 9:969-978). Transport competent peptides can thus be used to enhance bioavailability of the amidate compounds. Di- or tripeptides having one or more amino acids in the D configuration are also compatible with peptide transport and can be utilized in the amidate compounds of this invention. Amino acids in the D configuration can be used to reduce the susceptibility of a di- or tripeptide to hydrolysis by proteases common to the brush border such as aminopeptidase N. In addition, di- or tripeptides alternatively are selected on the basis of their relative resistance to hydrolysis by proteases found in the lumen of the intestine. For example, tripeptides or polypeptides lacking asp and/or glu are poor substrates for aminopeptidase A, di- or tripeptides lacking amino acid residues on the N-terminal side of hydrophobic amino acids (leu, tyr, phe, val, trp) are poor substrates for endopeptidase, and peptides lacking a pro residue at the penultimate position at a free carboxyl terminus are poor substrates for carboxypeptidase P. Similar considerations can also be applied to the selection of peptides that are either relatively resistant or relatively susceptible to hydrolysis by cytosolic, renal, hepatic, serum or other peptidases. Such poorly cleaved polypeptide amidates are immunogens or are useful for bonding to proteins in order to prepare immunogens.

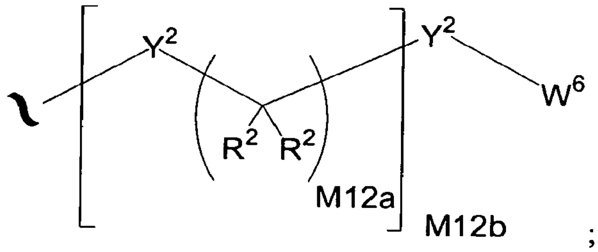
Specific Embodiments of the Invention

Specific values described for radicals, substituents, and ranges, as well as specific embodiments of the invention described herein, are for illustration only; they do not exclude other defined values or other values within defined ranges.

In one specific embodiment of the invention, the conjugate is a compound that is substituted with one or more phosphonate groups either directly or indirectly through a linker; and that is optionally substituted with one or more groups A^0; or a pharmaceutically acceptable salt thereof, wherein:

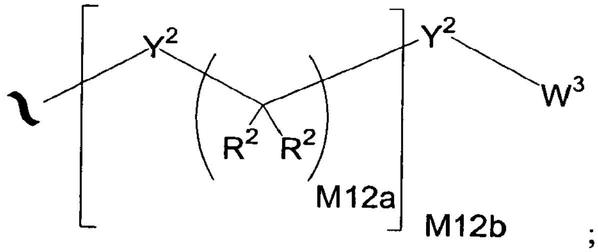
A^0 is A^1, A^2 or W^3;

A^1 is:


Y2
R2
R2
M12a
M12b
Y2
W6

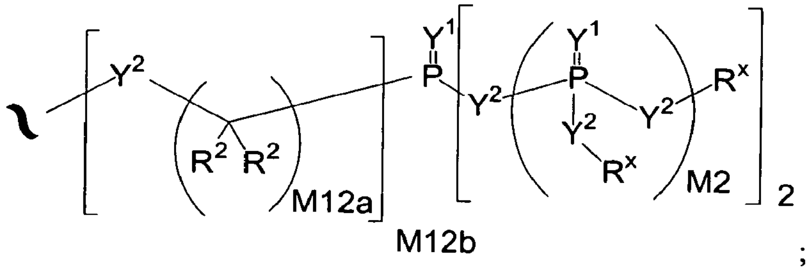
;

A^2 is:


Y2
R2
R2
M12a
M12b
Y2
W3

;

A^3 is:

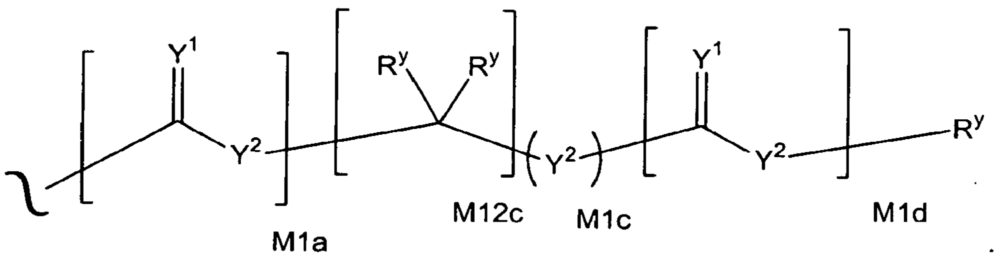

Y2
R2
R2
M12a
M12b
Y1
P
Y2
Y1
P
Y2
Rx
Y2
Rx
M2
2

;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$;

R^x is independently H, R^1, W^3, a protecting group, or the formula:



;

wherein:

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

M2 is 0, 1 or 2;

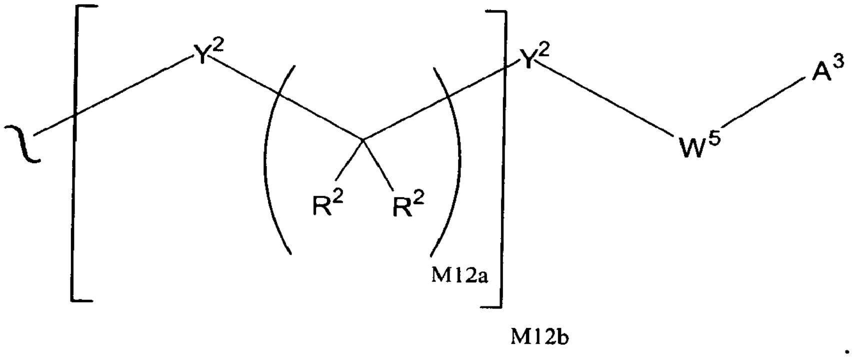
M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

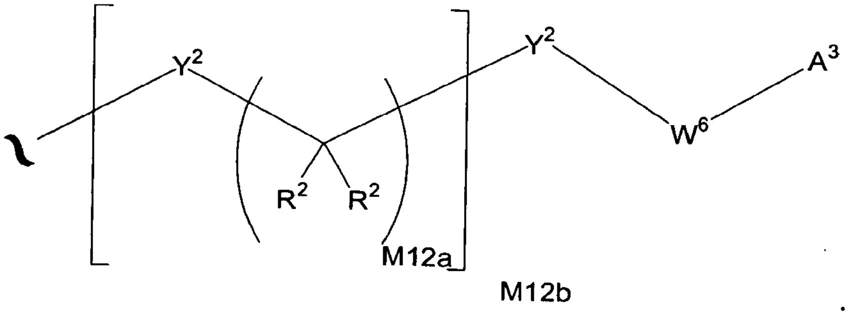
M1a, M1c, and M1d are independently 0 or 1; and

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

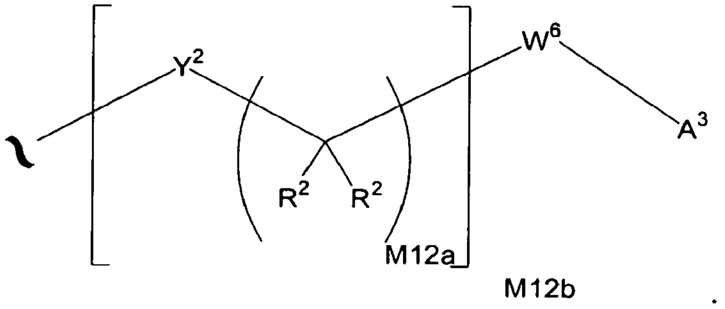
In another specific embodiment of the invention A^1 is of the formula:



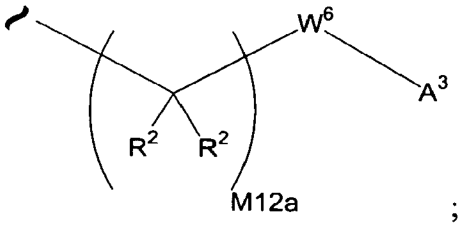
In another specific embodiment of the invention A^1 is of the formula:



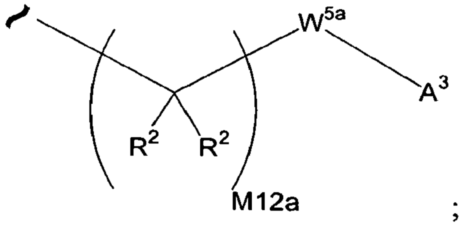
In another specific embodiment of the invention A^1 is of the formula:


Y2
W6
A3
R2
R2
M12a
M12b

In another specific embodiment of the invention A^1 is of the formula:

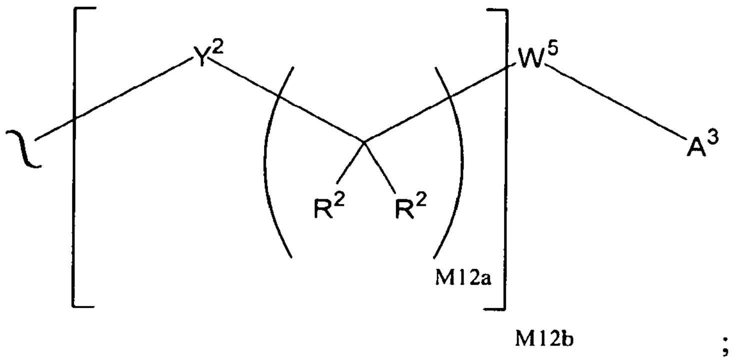

W6
A3
R2
R2
M12a

In another specific embodiment of the invention A^1 is of the formula:


W5a
A3
R2
R2
M12a

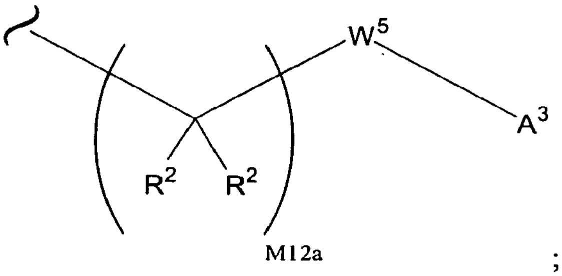
and W^{5a} is a carbocycle or a heterocycle where W^{5a} is independently substituted with 0 or 1 R^2 groups. A specific velue for M12a is 1.

In another specific embodiment of the invention A^1 is of the formula:


Y2
R2
R2
M12a
M12b
W5
A3

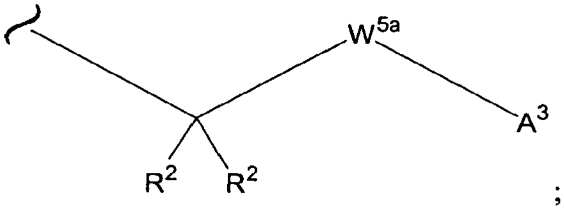
;

In another specific embodiment of the invention A^1 is of the formula:


W5
A3
R2
R2
M12a

;

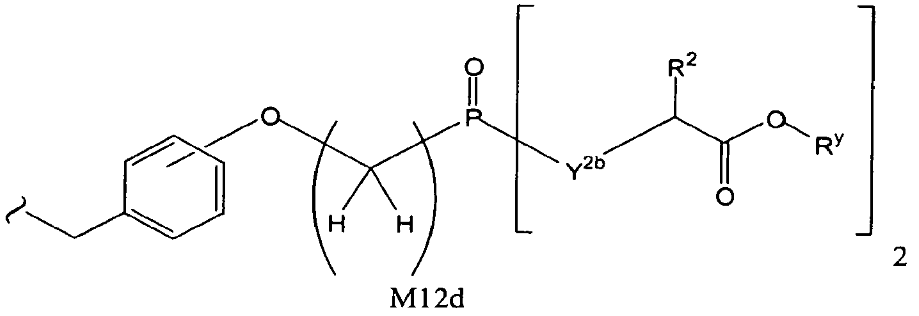
In another specific embodiment of the invention A^1 is of the formula:



;

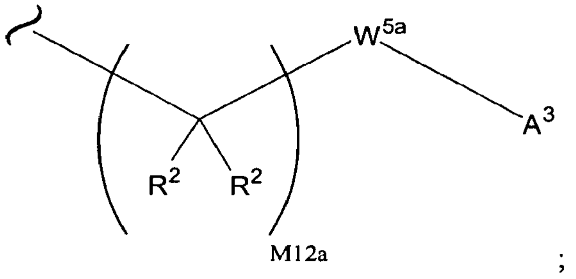
wherein W^{5a} is a carbocycle independently substituted with 0 or 1 R^2 groups;

In another specific embodiment of the invention A^1 is of the formula:


O
P
R2
O
Ry
Y2b
O
H
H
2
M12d

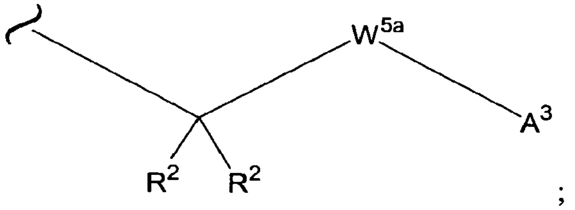
wherein Y^{2b} is O or $N(R^2)$; and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In another specific embodiment of the invention A^1 is of the formula:


W5a
A3
R2
R2
M12a
;

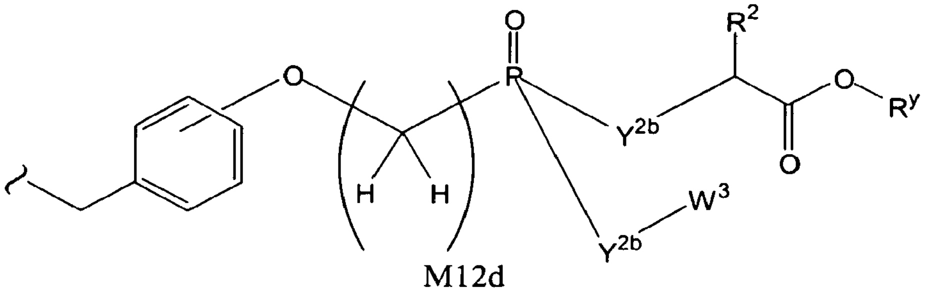
wherein W^{5a} is a carbocycle independently substituted with 0 or 1 R^2 groups;

In another specific embodiment of the invention A^1 is of the formula:



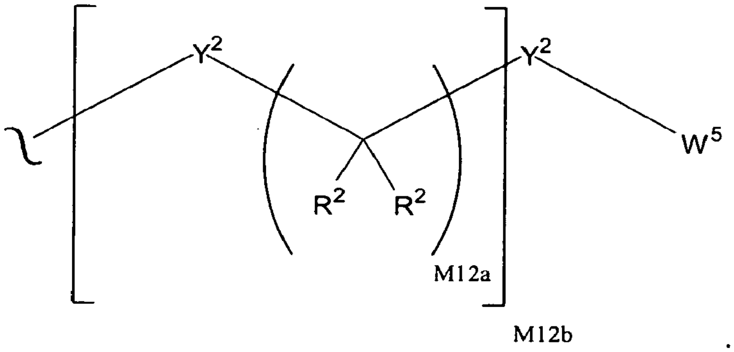
wherein W^{5a} is a carbocycle or heterocycle where W^{5a} is independently substituted with 0 or 1 R^2 groups.

In another specific embodiment of the invention A^1 is of the formula:

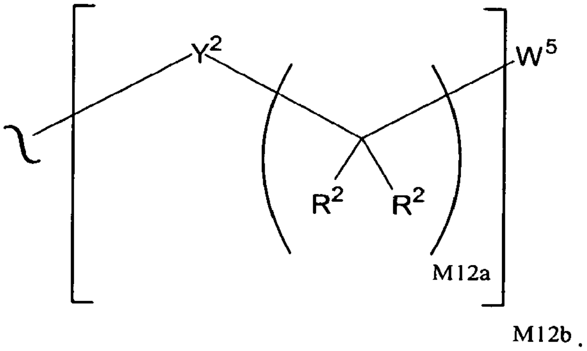

O
R2
P
O
Y2b
Ry
O
H
H
W3
Y2b
M12d

wherein Y^{2b} is O or $N(R^2)$; and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In a specific embodiment of the invention A^2 is of the formula:


Y2
Y2
W5
R2
R2
M12a
M12b

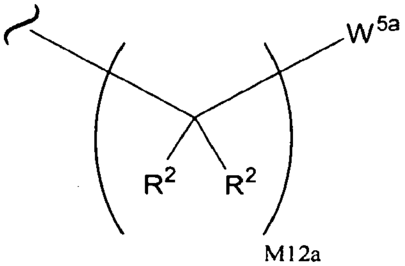
In another specific embodiment of the invention A^2 is of the formula:


Y2
W5
R2
R2
M12a
M12b

In another specific embodiment of the invention M12b is 1.

In another specific embodiment of the invention e M12b is 0, Y^2 is a bond and W^5 is a carbocycle or heterocycle where W^5 is optionally and independently substituted with 1, 2, or 3 R^2 groups.

In another specific embodiment of the invention A^2 is of the formula:



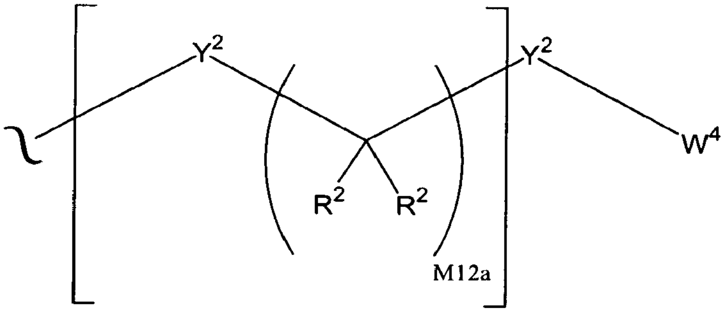
M12a ;

wherein W^{5a} is a carbocycle or heterocycle where W^{5a} is optionally and independently substituted with 1, 2, or 3 R^2 groups.

In another specific embodiment of the invention M12a is 1.

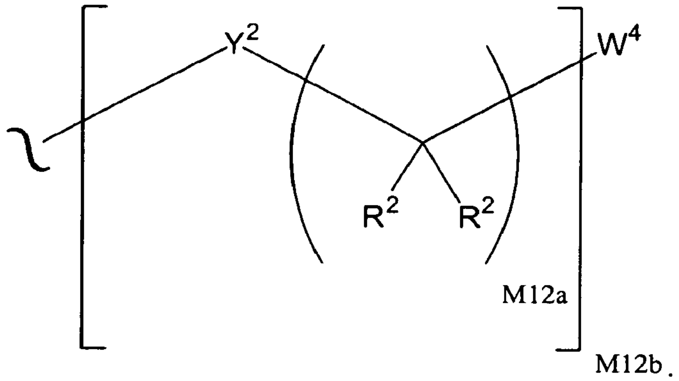
In another specific embodiment of the invention A^2 is selected from phenyl, substituted phenyl, benzyl, substituted benzyl, pyridyl and substituted pyridyl.

In another specific embodiment of the invention A^2 is of the formula:



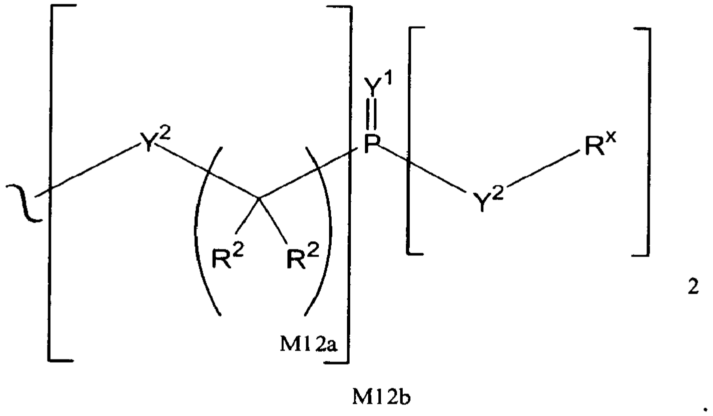
M12b

In another specific embodiment of the invention A^2 is of the formula:

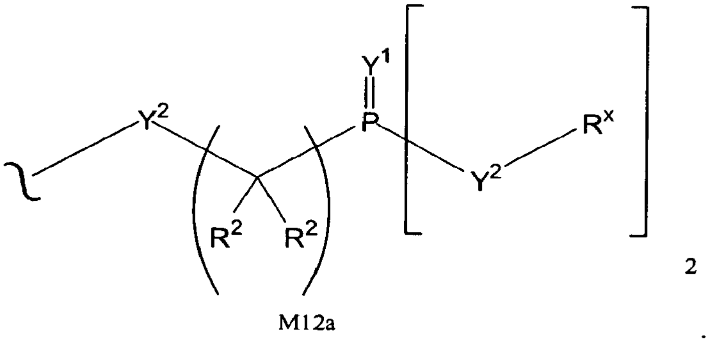

Y2
W4
R2
R2
M12a
M12b.

In another specific embodiment of the invention M12b is 1.

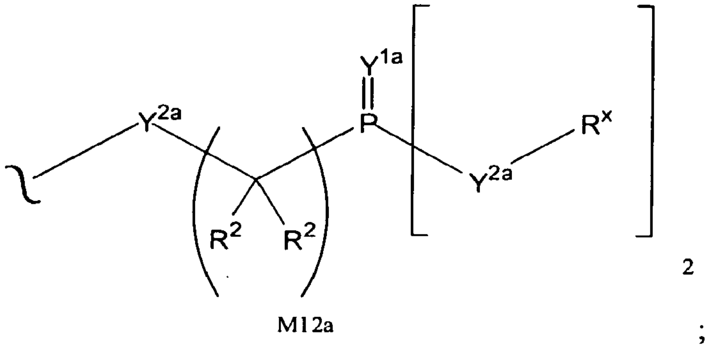
In a specific embodiment of the invention A^3 is of the formula:


Y1
P
Y2
Rx
Y2
R2
R2
M12a
M12b
2

In another specific embodiment of the invention A^3 is of the formula:


Y1
P
Y2
Rx
Y2
R2
R2
M12a
2

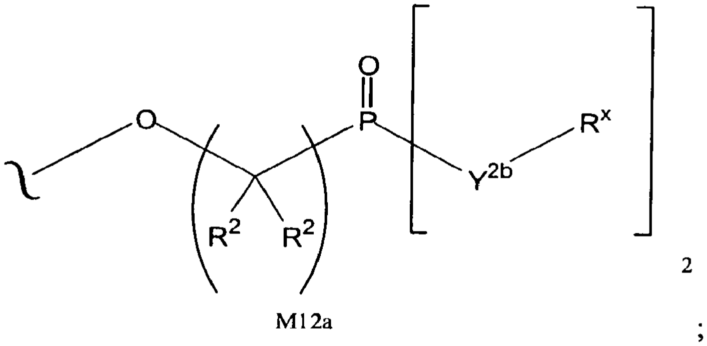
In another specific embodiment of the invention A^3 is of the formula:


Y1a
Y2a
P
Rx
Y2a
R2
R2
M12a
2

;

wherein Y^{1a} is O or S; and Y^{2a} is O, $N(R^x)$ or S.

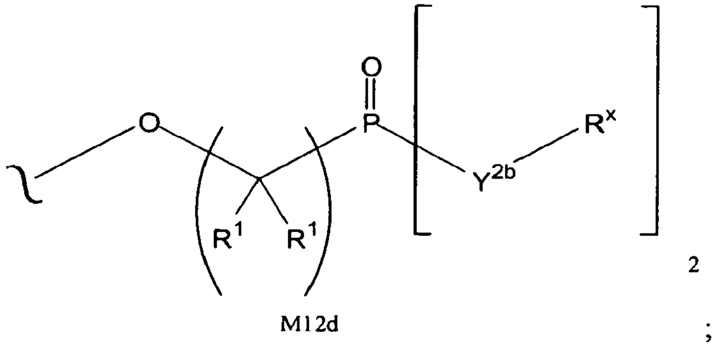
In another specific embodiment of the invention A^3 is of the formula:


O
O
P
Rx
Y2b
R2
R2
M12a
2

;

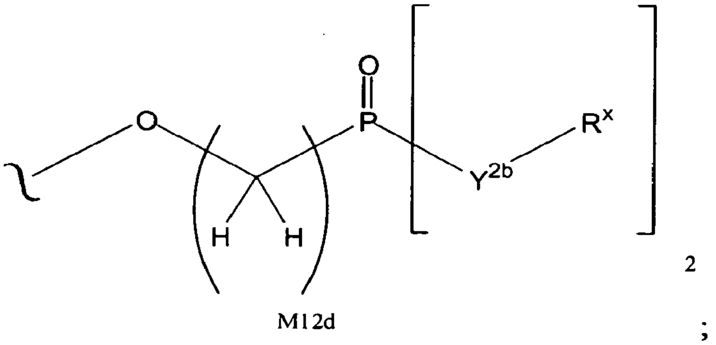
wherein Y^{2b} is O or $N(R^x)$.

In another specific embodiment of the invention A^3 is of the formula:



wherein Y^{2b} is O or $N(R^x)$; and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

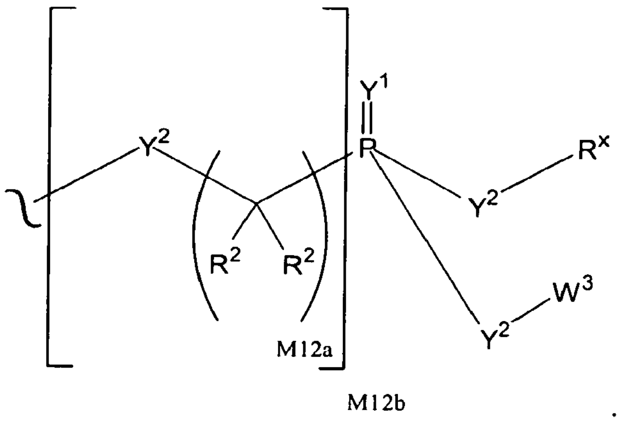
In another specific embodiment of the invention A^3 is of the formula:



wherein Y^{2b} is O or $N(R^x)$; and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

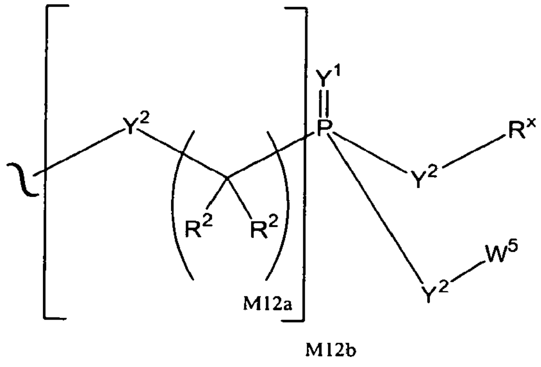
In another specific embodiment of the invention M12d is 1.

In another specific embodiment of the invention A^3 is of the formula:


Y1
Y2
Rx
Y2
R2
R2
W3
Y2
M12a
M12b

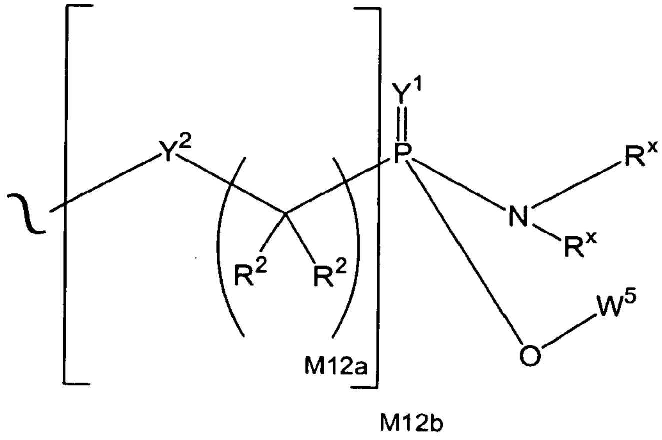
.

In another specific embodiment of the invention A^3 is of the formula:


Y1
Y2
Rx
Y2
R2
R2
W5
Y2
M12a
M12b

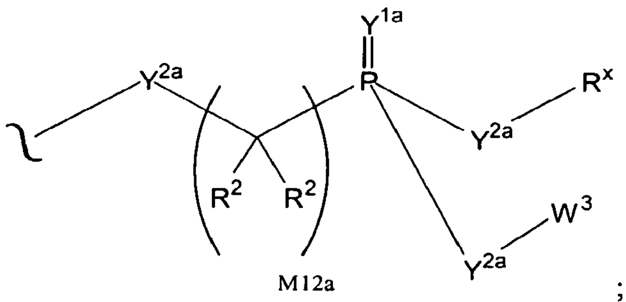
In another specific embodiment of the invention W^5 is a carbocycle.

In another specific embodiment of the invention A^3 is of the formula:


Y1
Y2
Rx
N
Rx
R2
R2
W5
O
M12a
M12b

In another specific embodiment of the invention W^5 is phenyl.

In another specific embodiment of the invention A^3 is of the formula:

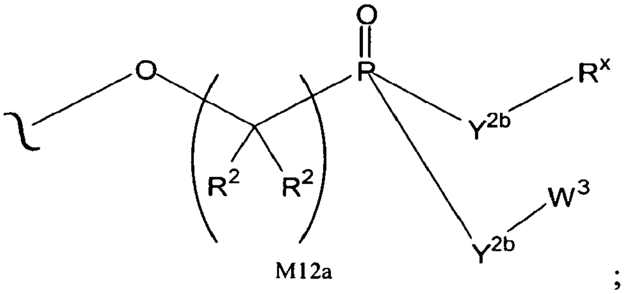


Y1a
Y2a
P
Rx
Y2a
R2
R2
W3
Y2a
M12a

;

wherein Y^{1a} is O or S; and Y^{2a} is O, N(R^x) or S.

In another specific embodiment of the invention A^3 is of the formula:

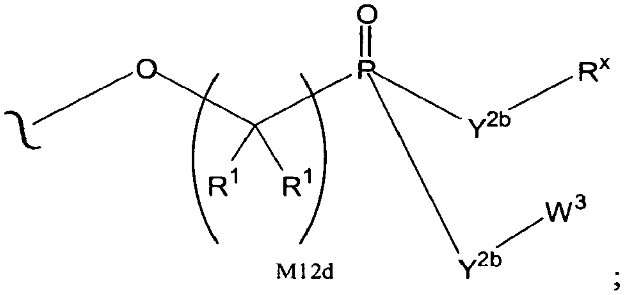


O
O
P
Rx
Y2b
R2
R2
W3
Y2b
M12a

;

wherein Y^{2b} is O or N(R^x).

In another specific embodiment of the invention A^3 is of the formula:



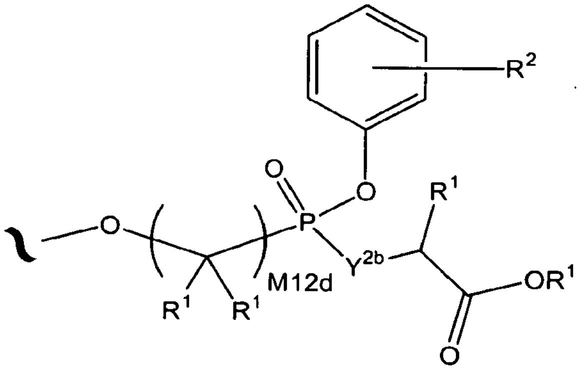
O
O
P
Rx
Y2b
R1
R1
W3
Y2b
M12d

;

wherein Y^{2b} is O or N(R^x); and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In another specific embodiment of the invention R^1 is H.

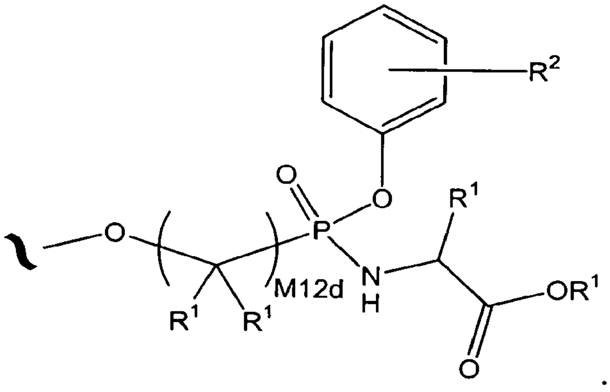
In another specific embodiment of the invention A^3 is of the formula:



R2
O
O
R1
O
P
Y2b
OR1
M12d
R1
R1
O

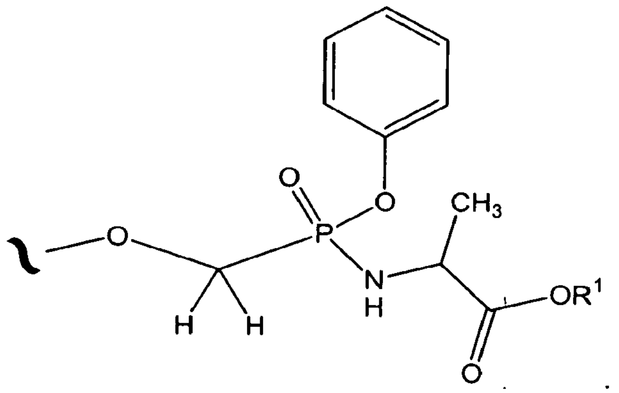
wherein the phenyl carbocycle is substituted with 0, 1, 2, or 3 R^2 groups.

In another specific embodiment of the invention A^3 is of the formula:



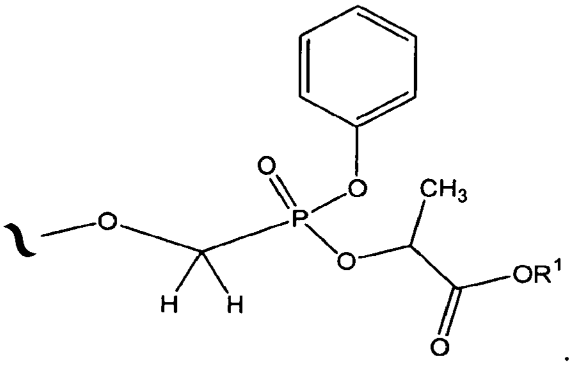
R2
O
O
R1
O
P
N
H
OR1
M12d
R1
R1
O

In another specific embodiment of the invention A^3 is of the formula:

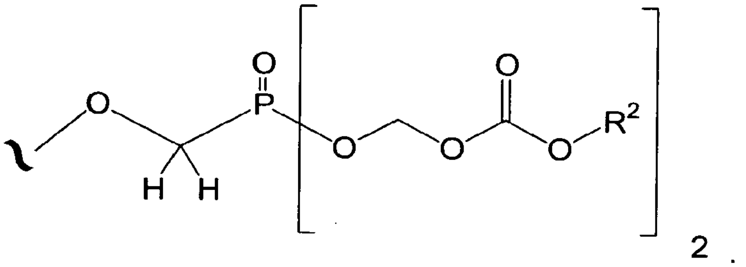


O
O
CH3
O
P
N
H
OR1
H
H
O

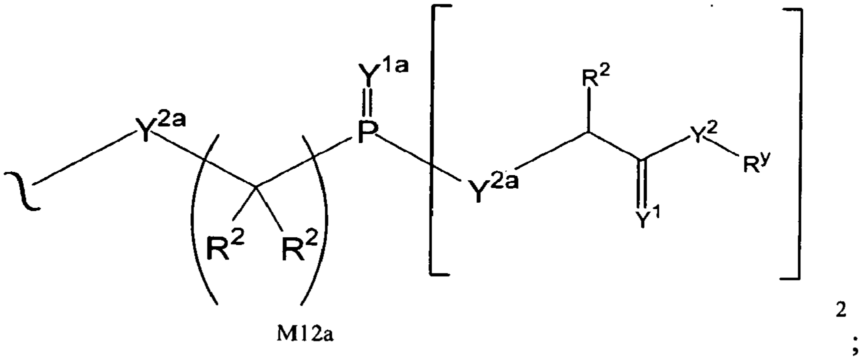
In another specific embodiment of the invention A^3 is of the formula:


O
O
P
O
CH3
OR1
O
H
H
O

In another specific embodiment of the invention A^3 is of the formula:

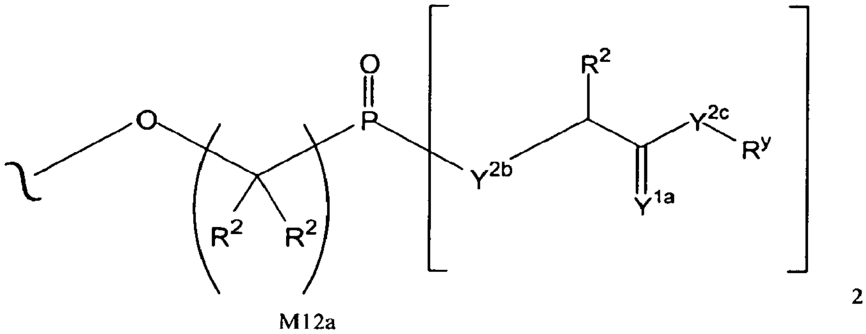

O
P
O
O
H
H
O
O
O
R2
2

In another specific embodiment of the invention A^3 is of the formula:


Y2a
Y1a
P
R2
R2
M12a
Y2a
R2
Y2
Ry
Y1
2

wherein Y^{1a} is O or S; and Y^{2a} is O, $N(R^2)$ or S.

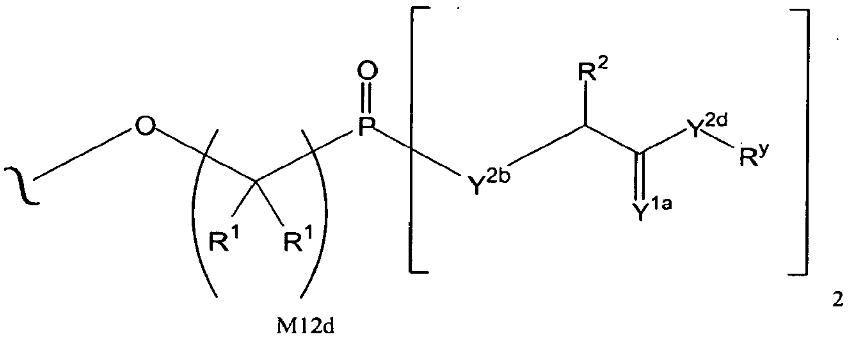
In another specific embodiment of the invention A^3 is of the formula:



;

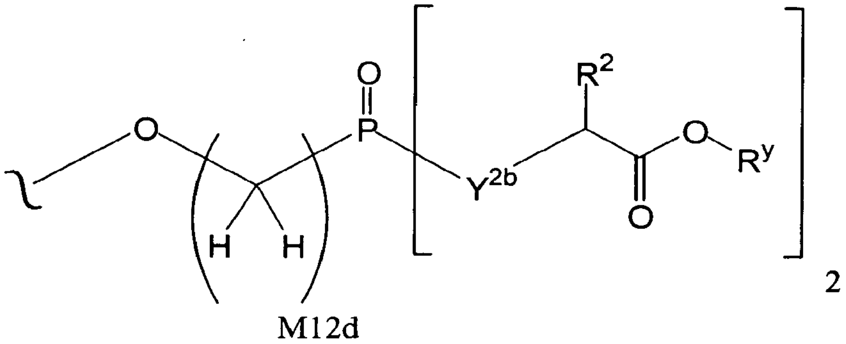
wherein Y^{1a} is O or S; Y^{2b} is O or $N(R^2)$; and Y^{2c} is O, $N(R^y)$ or S.

In another specific embodiment of the invention A^3 is of the formula:



wheren Y^{1a} is O or S; Y^{2b} is O or $N(R^2)$; Y^{2d} is O or $N(R^y)$; and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

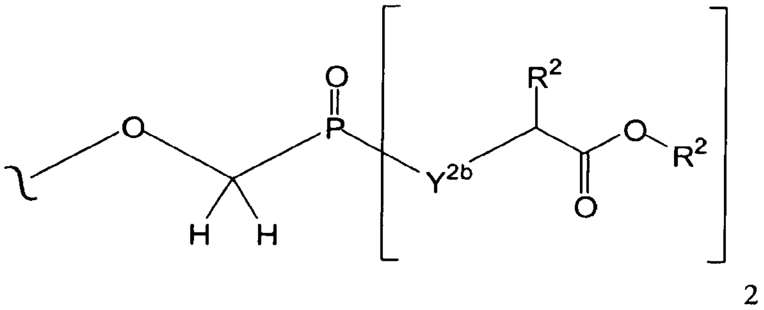
In another specific embodiment of the invention A^3 is of the formula:



;

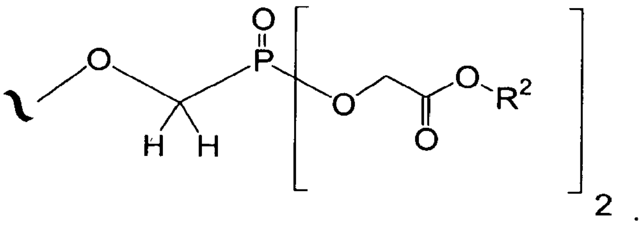
wherein Y^{2b} is O or $N(R^2)$; and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In another specific embodiment of the invention A^3 is of the formula:

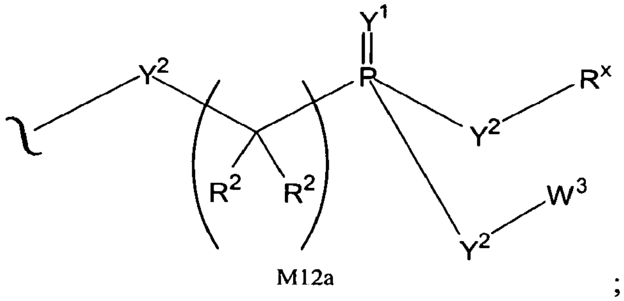


wherein Y^{2b} is O or $N(R^2)$.

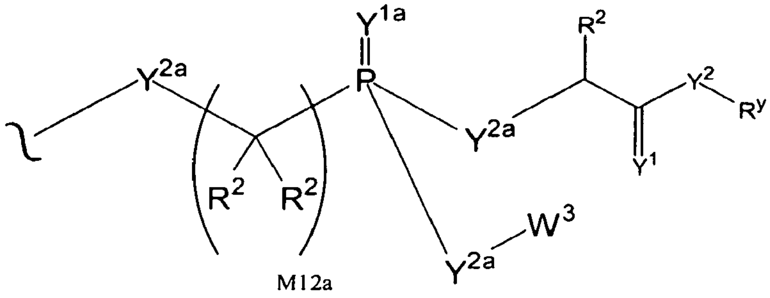
In another specific embodiment of the invention A^3 is of the formula:



In another specific embodiment of the invention A^3 is of the formula:



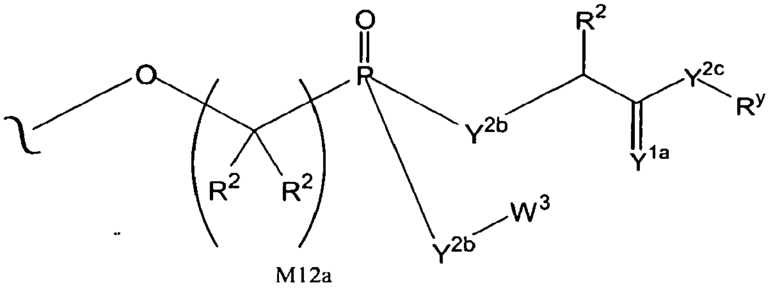
In another specific embodiment of the invention A^3 is of the formula:


Y1a
R2
Y2a
P
Y2
Ry
Y2a
Y1
R2
R2
W3
Y2a
M12a

;

wherein Y^{1a} is O or S; and Y^{2a} is O, $N(R^2)$ or S.

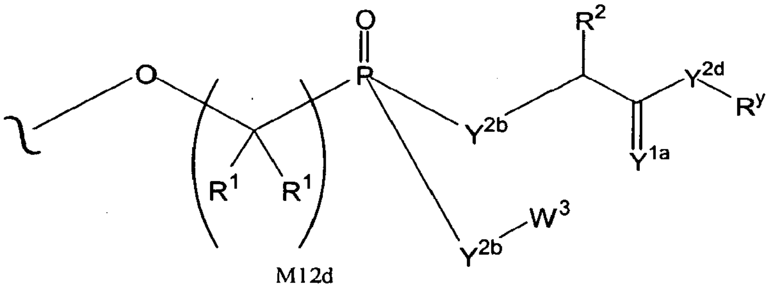
In another specific embodiment of the invention A^3 is of the formula:


O
R2
O
P
Y2c
Ry
Y2b
Y1a
R2
R2
W3
Y2b
M12a

;

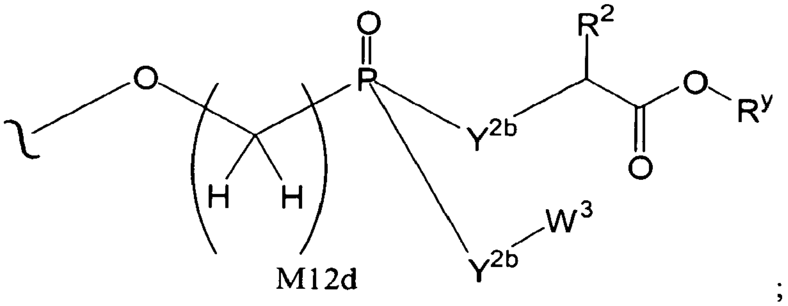
wherein Y^{1a} is O or S; Y^{2b} is O or $N(R^2)$; and Y^{2c} is O, $N(R^y)$ or S.

In another specific embodiment of the invention A^3 is of the formula:


O
R2
O
P
Y2d
Ry
Y2b
Y1a
R1
R1
W3
Y2b
M12d

wherein Y^{1a} is O or S; Y^{2b} is O or $N(R^2)$; Y^{2d} is O or $N(R^y)$; and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

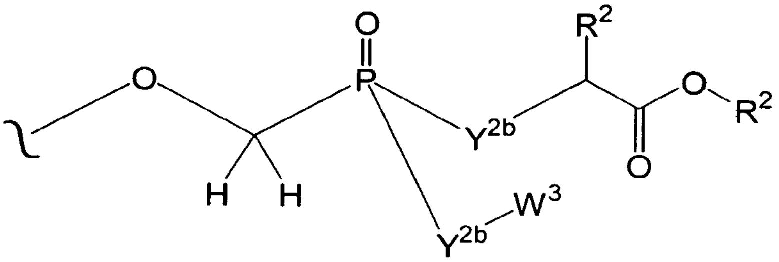
In another specific embodiment of the invention A^3 is of the formula:


O
R2
O
P
O
Ry
Y2b
O
H
H
W3
M12d
Y2b

;

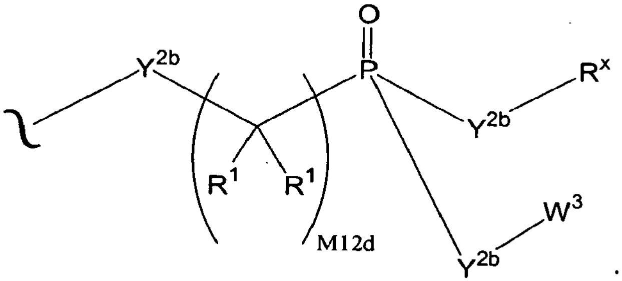
wherein Y^{2b} is O or $N(R^2)$; and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In another specific embodiment of the invention A^3 is of the formula:


O
R2
O
P
O
R2
Y2b
O
H
H
W3
Y2b

wherein Y^{2b} is O or $N(R^2)$.

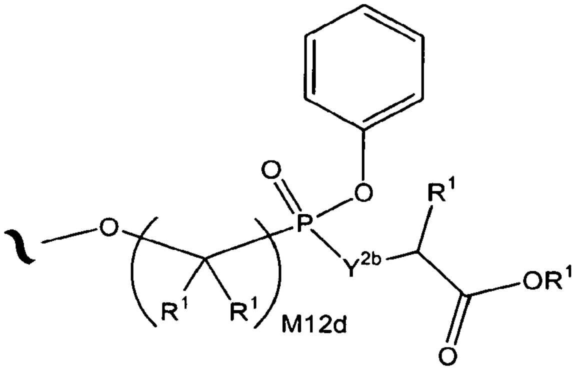
In another specific embodiment of the invention A^3 is of the formula:


O
Y2b
P
Rx
Y2b
R1
R1
W3
M12d
Y2b

;

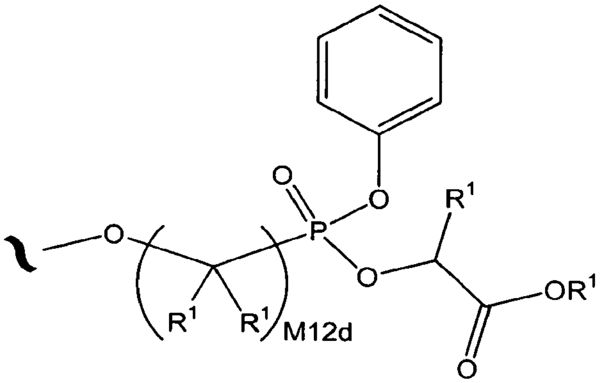
wherein: Y^{2b} is O or $N(R^x)$; and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In another specific embodiment of the invention A^3 is of the formula:



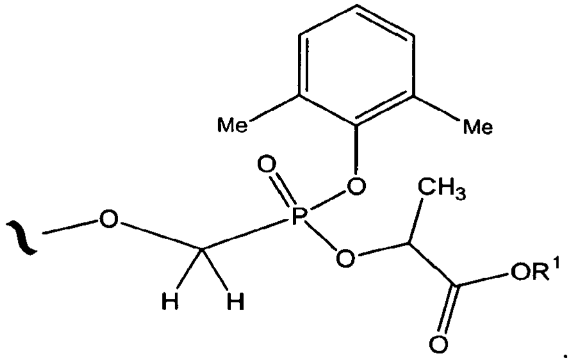
wherein the phenyl carbocycle is substituted with 0, 1, 2, or 3 R^2 groups.

In another specific embodiment of the invention A^3 is of the formula:

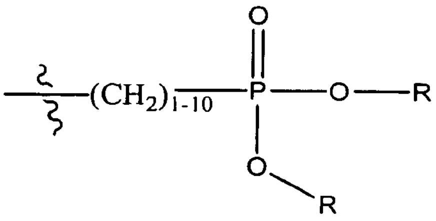


wherein the phenyl carbocycle is substituted with 0, 1, 2, or 3 R^2 groups.

In another specific embodiment of the invention A^3 is of the formula:

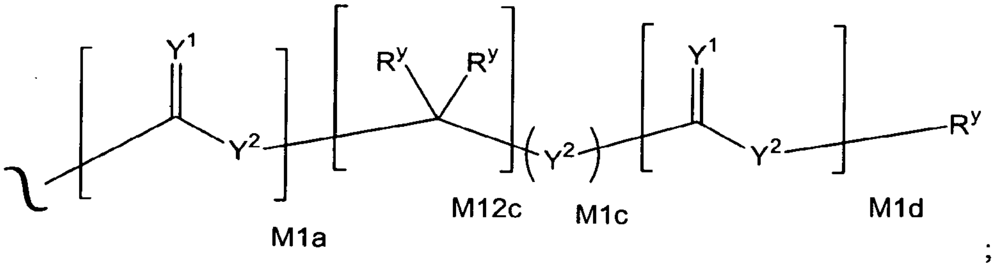


In a specific embodiment of the invention A^0 is of the formula:



wherein each R is independently $(C_1\text{-}C_6)$alkyl.

In a specific embodiment of the invention R^x is independently H, R^1, W^3, a protecting group, or the formula:



;

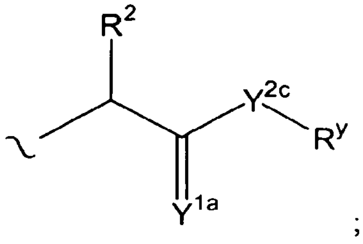
wherein:

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

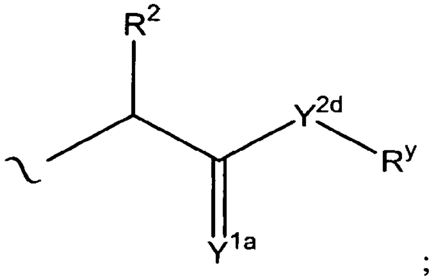
R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

In a specific embodiment of the invention R^x is of the formula:



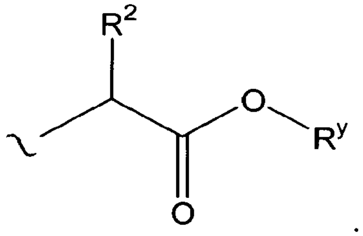
wherein Y^{1a} is O or S; and Y^{2c} is O, $N(R^y)$ or S.

In a specific embodiment of the invention R^x is of the formula:



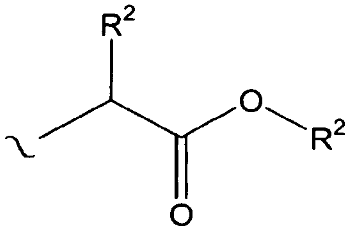
wherein Y^{1a} is O or S; and Y^{2d} is O or $N(R^y)$.

In a specific embodiment of the invention R^x is of the formula:

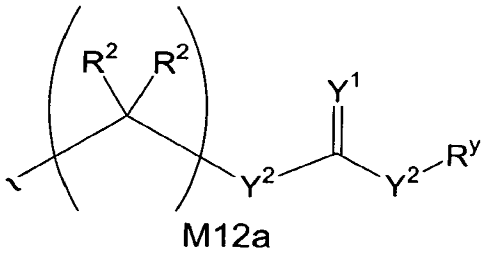


In a specific embodiment of the invention R^y is hydrogen or alkyl of 1 to 10 carbons.

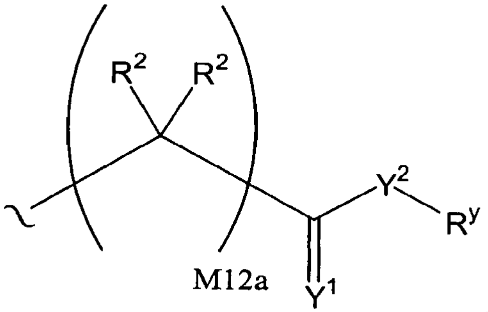
In a specific embodiment of the invention R^x is of the formula:



In a specific embodiment of the invention R^x is of the formula:


R2
R2
Y1
Y2
Y2
Ry
M12a

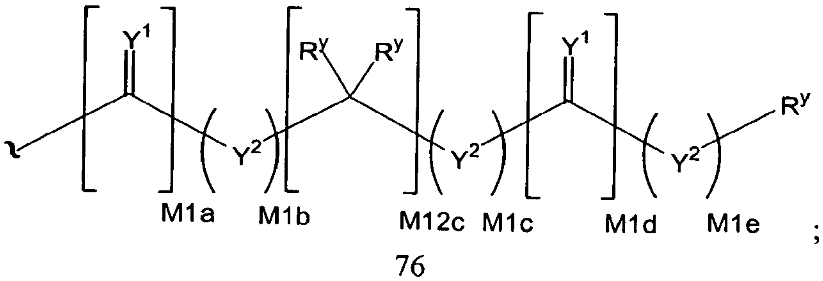
In a specific embodiment of the invention R^x is of the formula:


R2
R2
Y2
Ry
M12a
Y1

In a specific embodiment of the invention Y^1 is O or S

In a specific embodiment of the invention Y^2 is O, N(R^y) or S.

In one specific embodiment of the invention R^x is a group of the formula:


Y1
Y2
Ry
Ry
Y2
Y1
Y2
Ry
M1a
M1b
M12c
M1c
M1d
M1e

;

wherein:

m1a, m1b, m1c, m1d and m1e are independently 0 or 1;

m12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

R^y is H, W^3, R^2 or a protecting group;

provided that:

if m1a, m12c, and m1d are 0, then m1b, m1c and m1e are 0;

if m1a and m12c are 0 and m1d is not 0, then m1b and m1c are 0;

if m1a and m1d are 0 and m12c is not 0, then m1b and at least one of m1c and m1e are 0;

if m1a is 0 and m12c and m1d are not 0, then m1b is 0;

if m12c and m1d are 0 and m1a is not 0, then at least two of m1b, m1c and m1e are 0;

if m12c is 0 and m1a and m1d are not 0, then at least one of m1b and m1c are 0; and

if m1d is 0 and m1a and m12c are not 0, then at least one of m1c and m1e are 0.

In another specific embodiment, the invention provides a compound of the formula:

$$[\text{DRUG}]\text{-}(A^0)_{nn}$$

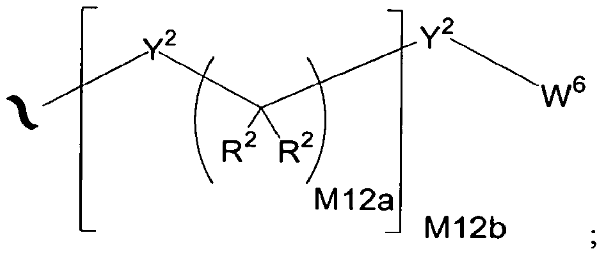
or a pharmaceutically acceptable salt thereof wherein,

DRUG is a compound of any one of formulae **500-511**

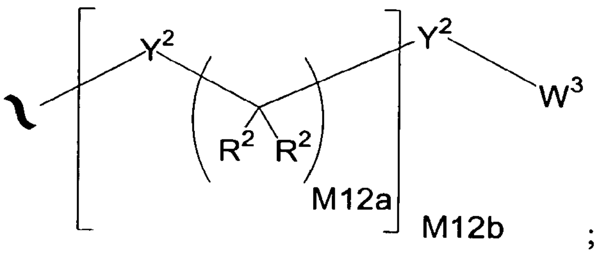
nn is 1, 2, or 3;

A^0 is A^1, A^2 or W^3 with the proviso that the compound includes at least one A^1;

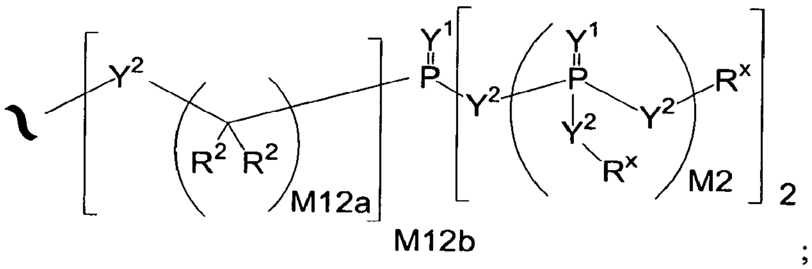
A^1 is:


Y2
Y2
W6
R2
R2
M12a
M12b
;

A^2 is:


Y2
Y2
W3
R2
R2
M12a
M12b
;

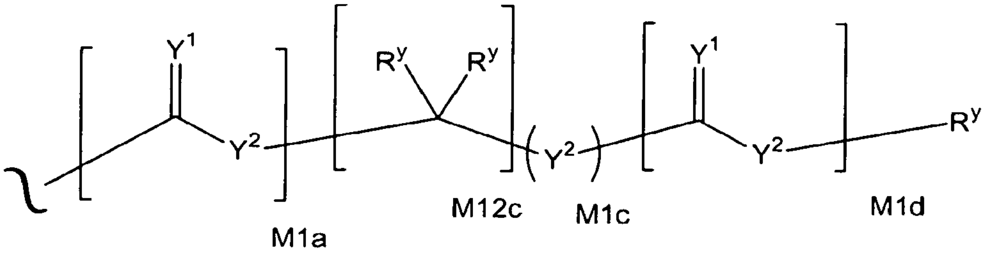
A^3 is:


Y2
R2
R2
M12a
M12b
Y1
P
Y2
Y1
P
Y2
Rx
Y2
Rx
M2
2
;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$;

R^x is independently H, R^1, W^3, a protecting group, or the formula:



;

wherein:

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1; and

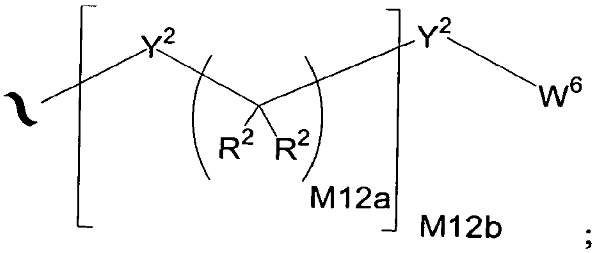
M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

In another specific embodiment, the invention provides a compound of the formula **1-36**:

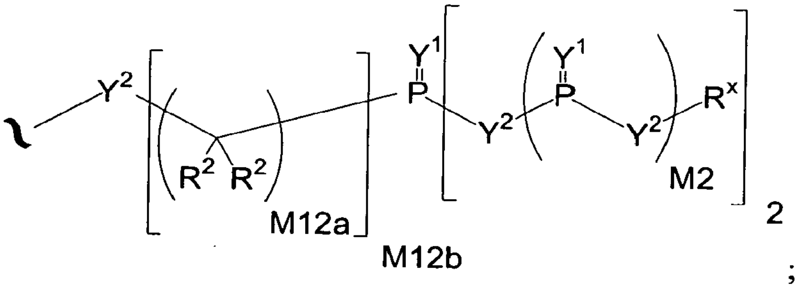
or a pharmaceutically acceptable salt or solvate thereof wherein:

A^0 is A^1;

A^1 is:



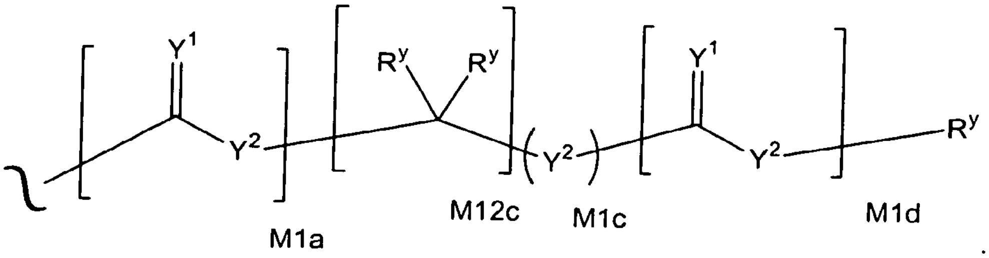
A^3 is:



Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$;

R^x is independently H, W^3, a protecting group, or the formula:



;

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

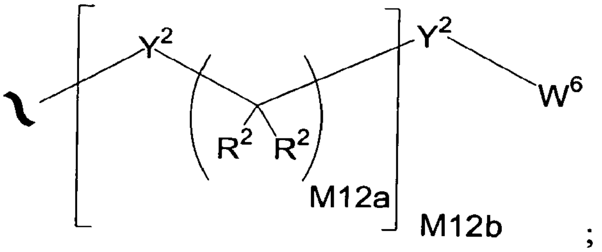
X^{50} is H F, or Cl; and

X^{51} is H or Cl.

The present invention also provides a compound of any one of formulae **1-36** wherein:

A^0 is A^1;

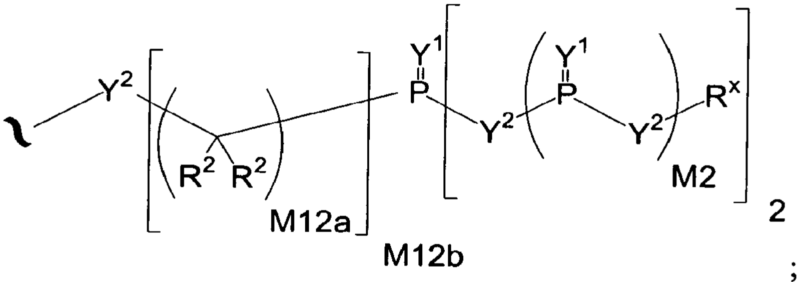
A^1 is:



Y2
Y2
W6
R2
R2
M12a
M12b

;

A^3 is:



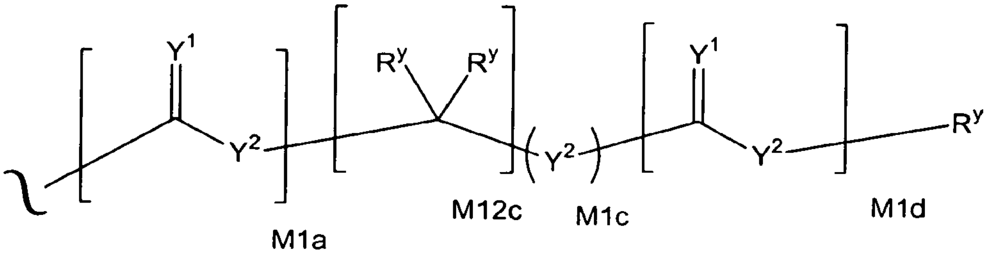
Y2
R2
R2
M12a
M12b
Y1
P
Y2
Y1
P
Y2
Rx
M2
2

;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$;

R^x is independently H, W^3, a protecting group, or the formula:



;

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

X^{50} is H F, or Cl; and

X^{51} is H or Cl.

In another specific embodiment, the invention provides a compound of the formula:

$$[\mathrm{DRUG}]\text{-}[\mathrm{L}\text{-}\mathrm{P}(=\mathrm{Y}^1)\text{-}\mathrm{Y}^2\text{-}\mathrm{R}^x]_{nn}$$

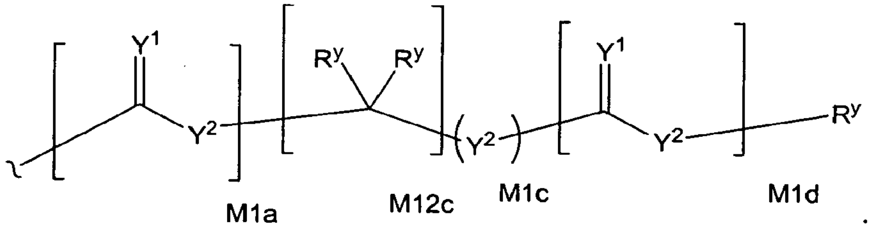
or a pharmaceutically acceptable salt thereof wherein,

DRUG is a compound of any one of **500-511**;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$;

R^x is independently H, W^3, a protecting group, or the formula:



;

R^y is independently H, W^3, R^2 or a protecting group;

R^2 is independently H, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

M2 is 1, 2, or 3;

M1a, M1c, and M1d are independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

nn is 1, 2, or 3; and

L is a linking group.

In another specific embodiment, the invention provides a compound of which is a compound of the formula:

$$[DRUG]\text{-}(A^0)_{nn}$$

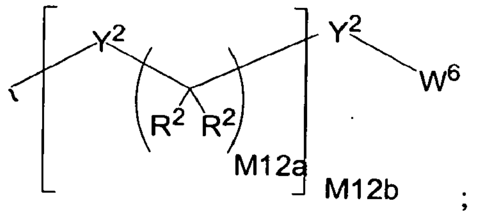
or a pharmaceutically acceptable salt thereof wherein,

DRUG is a compound of any one of formulae **500-511**;

nn is 1, 2, or 3;

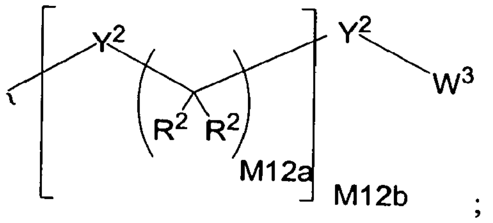
A^0 is A^1, A^2, or W^3 with the proviso that the compound includes at least one A^1;

A^1 is:



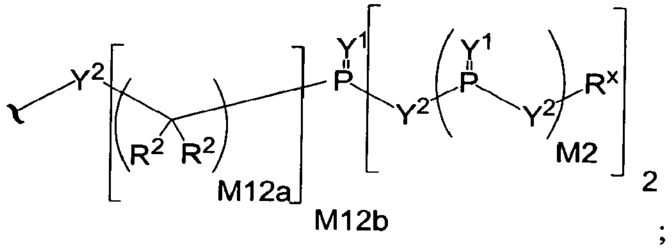
Y2
Y2
W6
R2
R2
M12a
M12b
;

A^2 is:



Y2
Y2
W3
R2
R2
M12a
M12b
;

A^3 is:

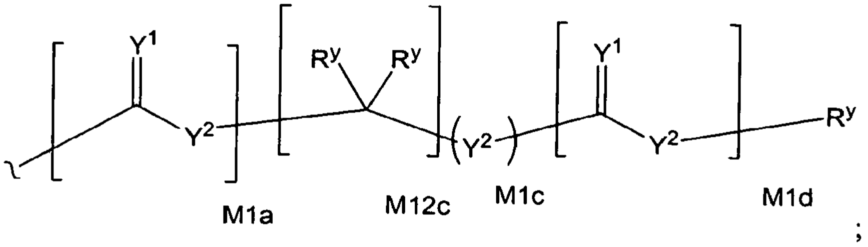


Y2
Y1
P
Y1
P
Y2
Y2
R^x
R2
R2
M12a
M12b
M2
2
;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$;

R^x is independently H, W^3, a protecting group, or the formula:



Y1
Y2
R^y
R^y
Y2
Y1
Y2
R^y
M1a
M12c
M1c
M1d
;

R^y is independently H, W^3, R^2 or a protecting group;

R^2 is independently H, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

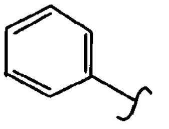
M1a, M1c, and M1d are independently 0 or 1; and

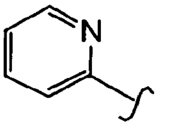
M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

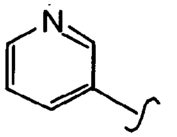
In compounds of the invention W^5 carbocycles and W^5 heterocycles may be independently substituted with 0 to 3 R^2 groups. W^5 may be a saturated, unsaturated or aromatic ring comprising a mono- or bicyclic carbocycle or heterocycle. W^5 may have 3 to 10 ring atoms, *e.g.*, 3 to 7 ring atoms. The W^5 rings are saturated when containing 3 ring atoms, saturated or mono-unsaturated when containing 4 ring atoms, saturated, or mono- or di-unsaturated when containing 5 ring atoms, and saturated, mono- or di-unsaturated, or aromatic when containing 6 ring atoms.

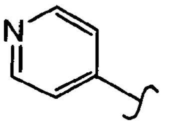
A W^5 heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S). W^5 heterocyclic monocycles may have 3 to 6 ring atoms (2 to 5 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S); or 5 or 6 ring atoms (3 to 5 carbon atoms and 1 to 2 heteroatoms selected from N and S). W^5 heterocyclic bicycles have 7 to 10 ring atoms (6 to 9 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S) arranged as a bicyclo [4,5], [5,5], [5,6], or [6,6] system; or 9 to 10 ring atoms (8 to 9 carbon atoms and 1 to 2 hetero atoms selected from N and S) arranged as a bicyclo [5,6] or [6,6] system. The W^5 heterocycle may be bonded to Y^2 through a carbon, nitrogen, sulfur or other atom by a stable covalent bond.

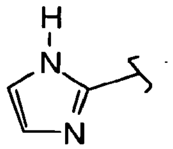
W^5 heterocycles include for example, pyridyl, dihydropyridyl isomers, piperidine, pyridazinyl, pyrimidinyl, pyrazinyl, s-triazinyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, furanyl, thiofuranyl, thienyl, and pyrrolyl. W^5 also includes, but is not limited to, examples such as:

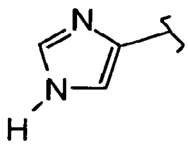
 ,

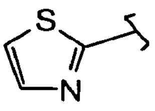
 ,

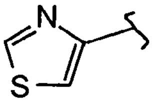
 ,

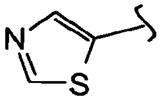
 ,

 ,

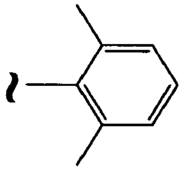
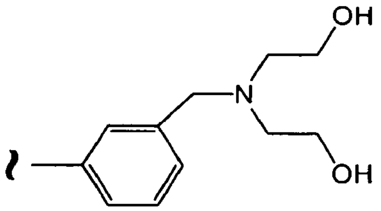
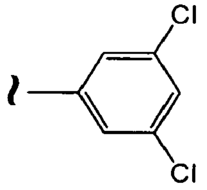
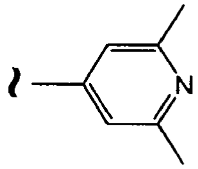
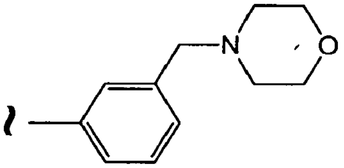
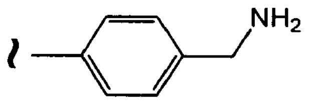
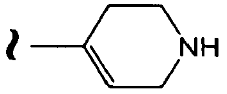
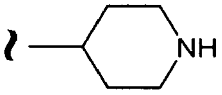
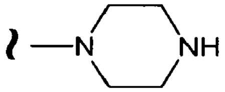
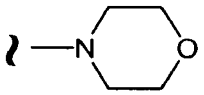
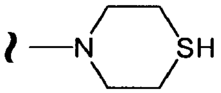
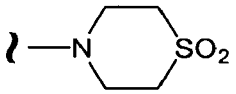
 ,

 ,

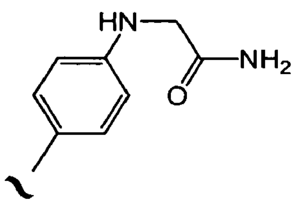
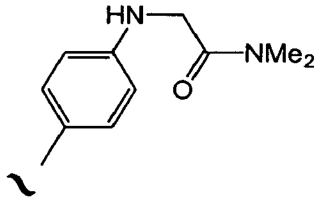
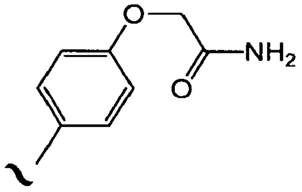
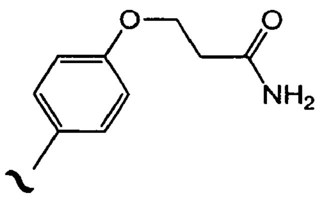
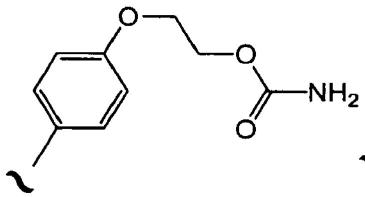
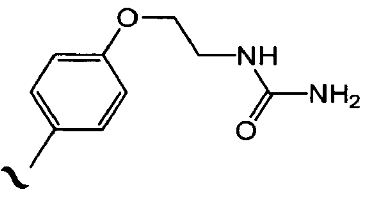
 , and

 .

W^5 carbocycles and heterocycles may be independently substituted with 0 to 3 R^2 groups, as defined above. For example, substituted W^5 carbocycles include:

Examples of substituted phenyl carbocycles include:

Linking Groups and Linkers

The invention provides conjugates that comprise a kinase inhibiting compound that is linked to one or more phosphonate groups either directly (e.g. through a covalent bond) or through a linking group (i.e. a linker). The nature of the linker is not critical provided it does not interfere with the ability of the phosphonate containing compound to function as a therapeutic agent. The phosphonate or the linker can be linked to the compound (*e.g.* a compound of **500-511**) at any synthetically feasible position on the compound by removing a hydrogen or any portion of the compound to provide an open valence for attachment of the phosphonate or the linker.

In one embodiment of the invention the linking group or linker (which can be designated "L") can include all or a portions of the group A^0, A^1, A^2, or W^3 described herein.

In another embodiment of the invention the linking group or linker has a molecular weight of from about 20 daltons to about 400 daltons.

In another embodiment of the invention the linking group or linker has a length of about 5 angstroms to about 300 angstroms.

In another embodiment of the invention the linking group or linker separates the DRUG and a $P(=Y^1)$ residue by about 5 angstroms to about 200 angstroms, inclusive, in length.

In another embodiment of the invention the linking group or linker is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 2 to 25 carbon atoms, wherein one or more (*e.g.* 1, 2, 3, or 4) of the carbon atoms is optionally replaced by (-O-), and wherein the chain is optionally substituted on carbon with one or more (*e.g.* 1, 2, 3, or 4) substituents selected from $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_6)$cycloalkyl, $(C_1\text{-}C_6)$alkanoyl, $(C_1\text{-}C_6)$alkanoyloxy, $(C_1\text{-}C_6)$alkoxycarbonyl, $(C_1\text{-}C_6)$alkylthio, azido, cyano, nitro, halo, hydroxy, oxo (=O), carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy.

In another embodiment of the invention the linking group or linker is of the formula W-A wherein A is $(C_1\text{-}C_{24})$alkyl, $(C_2\text{-}C_{24})$alkenyl, $(C_2\text{-}C_{24})$alkynyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_6\text{-}C_{10})$aryl or a combination thereof, wherein W is -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, $-S(O)_2-$, -

N(R)-, -C(=O)-, or a direct bond; wherein each R is independently H or (C_1-C_6)alkyl.

In another embodiment of the invention the linking group or linker is a divalent radical formed from a peptide.

In another embodiment of the invention the linking group or linker is a divalent radical formed from an amino acid.

In another embodiment of the invention the linking group or linker is a divalent radical formed from poly-L-glutamic acid, poly-L-aspartic acid, poly-L-histidine, poly-L-ornithine, poly-L-serine, poly-L-threonine, poly-L-tyrosine, poly-L-leucine, poly-L-lysine-L-phenylalanine, poly-L-lysine or poly-L-lysine-L-tyrosine.

In another embodiment of the invention the linking group or linker is of the formula W-$(CH_2)_n$ wherein, n is between about 1 and about 10; and W is -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -$S(O)_2$-, -C(=O)-, -N(R)-, or a direct bond; wherein each R is independently H or (C_1-C_6)alkyl.

In another embodiment of the invention the linking group or linker is methylene, ethylene, or propylene.

In another embodiment of the invention the linking group or linker is attached to the phosphonate group through a carbon atom of the linker.

Intracellular Targeting

The phosphonate group of the compounds of the invention may cleave *in vivo* in stages after they have reached the desired site of action, *i.e.* inside a cell. One mechanism of action inside a cell may entail a first cleavage, *e.g.* by esterase, to provide a negatively-charged "locked-in" intermediate. Cleavage of a terminal ester grouping in a compound of the invention thus affords an unstable intermediate which releases a negatively charged "locked in" intermediate.

After passage inside a cell, intracellular enzymatic cleavage or modification of the phosphonate or prodrug compound may result in an intracellular accumulation of the cleaved or modified compound by a “trapping” mechanism. The cleaved or modified compound may then be "locked-in" the cell by a significant change in charge, polarity, or other physical property change which decreases the rate at which the cleaved or modified compound can exit the cell, relative to the rate at which it entered as the phosphonate prodrug. Other mechanisms by which a therapeutic effect are achieved may be operative as well. Enzymes which are capable of an enzymatic activation mechanism with the phosphonate prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphatases.

From the foregoing, it will be apparent that many different drugs can be derivatized in accord with the present invention. Numerous such drugs are specifically mentioned herein. However, it should be understood that the discussion of drug families and their specific members for derivatization according to this invention is not intended to be exhaustive, but merely illustrative.

Kinase-Inhibitory Compounds

The compounds of the invention include those with kinase-inhibitory activity. The compounds of the inventions bear one or more (*e.g.* 1, 2, 3, or 4) phosphonate groups, which may be a prodrug moiety.

The term "kinase-inhibitory compound" includes those compounds that inhibit the activity of at least one kinase. In particular, the compounds include Gefitinib, imatinib, erlotinib, vatalanib, alvocidib, CEP-701, GLEEVEC, midostaurin, MLN-518, PD-184352, doramapimod, BAY-43-9006, and CP-690,550.

Typically, compounds of the invention have a molecular weight of from about 400 amu to about 10,000 amu; in a specific embodiment of the invention, compounds have a molecular weight of less than about 5000 amu; in another specific embodiment of the invention, compounds have a molecular weight of less than about 2500 amu; in another specific embodiment of the invention, compounds have a molecular weight of less than about 1000 amu; in another specific embodiment of the invention, compounds have a molecular weight of less than about 800 amu; in another specific embodiment of the invention, compounds have a molecular weight of less than about 600 amu; and in another specific embodiment of the invention, compounds have a molecular weight of less than about 600 amu and a molecular weight of greater than about 400 amu.

The compounds of the invention also typically have a logD(polarity) less than about 5. In one embodiment the invention provides compounds having a logD less than about 4; in another one embodiment the invention provides compounds having a logD less than about 3; in another one embodiment the invention provides compounds having a logD greater than about -5; in another one embodiment the invention provides compounds having a logD greater than about -3; and in another one embodiment the invention provides compounds having a logD greater than about 0 and less than about 3.

Selected substituents within the compounds of the invention are present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number may be present in any given claim. For example, R^x contains a R^y substituent. R^y can be R^2, which in turn can be R^3. If R^3 is selected to be R^{3c}, then a second instance of R^x can be selected. One of ordinary skill in the art of medicinal chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

By way of example and not limitation, W^3, R^y and R^3 are all recursive substituents in certain claims. Typically, each of these may independently occur 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0, times in a given claim. More typically, each of these may independently occur 12 or fewer times in a given claim. More typically yet, W^3 will occur 0 to 8 times, R^y will occur 0 to 6 times and R^3 will occur 0 to 10 times in a given claim. Even more typically, W^3 will occur 0 to 6 times, R^y will occur 0 to 4 times and R^3 will occur 0 to 8 times in a given claim.

Recursive substituents are an intended aspect of the invention. One of ordinary skill in the art of medicinal chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in an claim of the invention, the total number will be determined as set forth above.

Whenever a compound described herein is substituted with more than one of the same designated group, *e.g.*, "R^1" or "R^{6a}", then it will be understood that the groups may be the same or different, *i.e.*, each group is independently selected. Wavy lines indicate the site of covalent bond attachments to the adjoining groups, moieties, or atoms.

In one embodiment of the invention, the compound is in an isolated and purified form. Generally, the term "isolated and purified" means that the compound is substantially free from biological materials (*e.g.* blood, tissue, cells, etc.). In one specific embodiment of the invention, the term means that the compound or conjugate of the invention is at least about 50 wt.% free from biological materials; in another specific embodiment, the term means that the compound or conjugate of the invention is at least about 75 wt.% free from biological materials; in another specific embodiment, the term means that the compound or conjugate of the invention is at least about 90 wt.% free from biological materials; in another specific embodiment, the term means that the compound or conjugate of the invention is at least about 98 wt.% free from biological materials; and in another embodiment, the term means that the compound or conjugate of the invention is at least about 99 wt.% free from biological materials. In another specific embodiment, the invention provides a compound or conjugate of the invention that has been synthetically prepared (*e.g.*, *ex vivo*).

In one embodiment of the invention, the compound is not an anti-inflammatory compound; in another embodiment the compound is not an anti-infective; in another embodiment the compound is not a compound that is active against immune-mediated conditions; in another embodiment the compound is not a compound that is active against metabolic diseases; in another embodiment the compound is not an antiviral agent; in another embodiment the compound is not a nucleoside; in another embodiment the compound is not a IMPDH inhibitor; in another embodiment the compound is not an antimetabolite; in another embodiment the compound is not a PNP inhibitor; in another embodiment the compound inhibits a serine/threonine kinase, tyrosine kinase, Bcr-Abl kinase, cyclin-dependent kinase, Flt3 tyrosine kinase, MAP Erk kinase, JAK3 kinase, VEGF receptor kinase, PDGF receptor tyrosine kinase, protein kinase C, insulin receptor tyrosine kinase, or an EGF receptor tyrosine kinase; in another embodiment the compound is not Gefitinib, imatinib, erlotinib, vatalanib, alvocidib, CEP-701, GLEEVEC, midostaurin, MLN-518, PD-184352, doramapimod, BAY-43-9006, or CP-690,550; in another embodiment the compound is not a substituted compound of any one of formulae **500-510**; in another embodiment the compound is not a substituted compound of formula **511**; in another embodiment the compound is not a compound of any one of formulae **1-33**; in another embodiment the compound is not a compound of formula **34** or **35**.

Cellular Accumulation

In one embodiment, the invention is provides compounds capable of accumulating in human PBMC (peripheral blood mononuclear cells). PBMC refer to blood cells having round lymphocytes and monocytes. Physiologically, PBMC are critical components of the mechanism against infection. PBMC may be isolated from heparinized whole blood of normal healthy donors or buffy coats, by standard density gradient centrifugation and harvested from the interface, washed (*e.g.* phosphate-buffered saline) and stored in freezing medium. PBMC may be cultured in multi-well plates. At various times of culture, supernatant may be either removed for assessment, or cells may be harvested and analyzed (Smith R. etal (2003) *Blood* 102(7):2532-2540). The compounds of this claim may further comprise a phosphonate or phosphonate prodrug. More typically, the phosphonate or phosphonate prodrug can have the structure A^3 as described herein.

Typically, compounds of the invention demonstrate improved intracellular half-life of the compounds or intracellular metabolites of the compounds in human PBMC when compared to analogs of the compounds not having the phosphonate or phosphonate prodrug. Typically, the half-life is improved by at least about 50%, more typically at least in the range 50-100%, still more typically at least about 100%, more typically yet greater than about 100%.

In one embodiment of the invention the intracellular half-life of a metabolite of the compound in human PBMCs is improved when compared to an analog of the compound not having the phosphonate or phosphonate prodrug. In such claims, the metabolite may be generated intracellularly, *e.g.* generated within human PBMC. The metabolite may be a product of the cleavage of a phosphonate prodrug within human PBMCs. The phosphonate prodrug may be cleaved to form a metabolite having at least one negative charge at physiological pH. The phosphonate prodrug may be enzymatically cleaved within human PBMC to form a phosphonate having at least one active hydrogen atom of the form P-OH.

Stereoisomers

The compounds of the invention may have chiral centers, *e.g.*, chiral carbon or phosphorus atoms. The compounds of the invention thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds of the invention include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures are separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, *e.g.*, acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

The compounds of the invention can also exist as tautomeric isomers in certain cases. All though only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the iinvention. For example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

Salts and Hydrates

The compositions of this invention optionally comprise salts of the compounds herein, especially pharmaceutically acceptable non-toxic salts containing, for example, Na^+, Li^+, K^+, Ca^{+2} and Mg^{+2}. Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid. Monovalent salts are preferred if a water soluble salt is desired.

Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing Li^+, Na^+, and K^+. A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

In addition, salts may be formed from acid addition of certain organic and inorganic acids, *e.g.*, HCl, HBr, H_2SO_4, H_3PO_4 or organic sulfonic acids, to basic centers, typically amines, or to acidic groups. Finally, it is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Also included within the scope of this invention are the salts of the parental compounds with one or more amino acids. Any of the amino acids described above are suitable, especially the naturally-occurring amino acids found as protein components, although the amino acid typically is one bearing a side chain with a basic or acidic group, *e.g.*, lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

Methods of Kinase Inhibition

Another aspect of the invention relates to methods of inhibiting the activity of at least one kinase comprising the step of treating a sample suspected of containing a kinase with a composition of the invention.

Compositions of the invention may act as kinase inhibitors, as intermediates for such inhibitors, or have other utilities as described below. The inhibitors will bind to locations on the surface or in a cavity of at least one kinase. Compositions binding the kinase may bind with varying degrees of reversibility. Those compounds binding substantially irreversibly are ideal candidates for use in this method of the invention. Once labeled, the substantially irreversibly binding compositions are useful as probes for the detection of a kinase. Accordingly, the invention relates to methods of detecting kinase in a sample suspected of containing kinase comprising the steps of: treating a sample suspected of containing kinase with a composition comprising a compound of the invention bound to a label; and observing the effect of the sample on the activity of the label. Suitable labels are well known in the diagnostics field and include stable free radicals, fluorophores, radioisotopes, enzymes, chemiluminescent groups and chromogens. The compounds herein are labeled in conventional fashion using functional groups such as hydroxyl or amino.

Within the context of the invention samples suspected of containing at least one kinase include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing a kinase. Samples can be contained in any medium including water and organic solvent/water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

The treating step of the invention comprises adding the composition of the invention to the sample or it comprises adding a precursor of the composition to the sample. The addition step comprises any method of administration as described above.

If desired, the activity of the kinase after application of the composition can be observed by any method including direct and indirect methods of detecting kinase activity. Quantitative, qualitative, and semiquantitative methods of determining kinase activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

Many organisms contain kinases. The compounds of this invention are useful in the treatment or prophylaxis of conditions associated with kinase activation in animals or in man.

However, in screening compounds capable of inhibiting kinase it should be kept in mind that the results of enzyme assays may not correlate with cell culture assays. Thus, a cell based assay should be the primary screening tool.

Screens for Kinase Inhibitors

Compositions of the invention are screened for inhibitory activity against a kinase by any of the conventional techniques for evaluating enzyme activity. Within the context of the invention, typically compositions are first screened for inhibition of kinase *in vitro* and compositions showing inhibitory activity are then screened for activity *in vivo*. Compositions having *in vitro* Ki (inhibitory constants) of less then about 5×10^{-6} M, typically less than about 1×10^{-7} M and preferably less than about 5×10^{-8} M are preferred for *in vivo* use.

Useful *in vitro* screens have been described in detail, *e.g.*, *Bioorg. Med. Chem. Lett.*, **2001**, *11*, 2775).

Pharmaceutical Formulations

The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice.

Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the Handbook of Pharmaceutical Excipients (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

For administration to the eye or other external tissues *e.g.*, mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, *i.e.* an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil.

Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

Pharmaceutical formulations according to the present invention comprise one or more compounds of the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (*e.g.*, lecithin), a condensation product of an alkylene oxide with a fatty acid (*e.g.*, polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (*e.g.*, heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (*e.g.*, polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of conditions associated with kinase activity.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention can also be formulated to provide controlled release of the active ingredient to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the active ingredient. Accordingly, the invention also provided compositions comprising one or more compounds of the invention formulated for sustained or controlled release.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses), the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day. Typically, from about 0.01 to about 10 mg/kg body weight per day. More typically, from about .01 to about 5 mg/kg body weight per day. More typically, from about .05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

Routes of Administration

One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

Combination Therapy

Active ingredients of the invention are also used in combination with other active ingredients. Such combinations are selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-properties of the combination.

It is also possible to combine any compound of the invention with one or more other active ingredients in a unitary dosage form for simultaneous or sequential administration to a patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

The combination therapy may provide "synergy" and "synergistic effect", *i.e.* the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, *e.g.*, in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, *i.e.* serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

Metabolites of the Compounds of the Invention

Also falling within the scope of this invention are the *in vivo* metabolic products of the compounds described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (*e.g.*, C^{14} or H^3) compound of the invention, administering it parenterally in a detectable dose (*e.g.*, greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, *e.g.*, by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no kinase inhibitory activity of their own.

Recipes and methods for determining stability of compounds in surrogate gastrointestinal secretions are known. Compounds are defined herein as stable in the gastrointestinal tract where less than about 50 mole percent of the protected groups are deprotected in surrogate intestinal or gastric juice upon incubation for 1 hour at 37 °C. Simply because the compounds are stable to the gastrointestinal tract does not mean that they cannot be hydrolyzed *in vivo*. The phosphonate prodrugs of the invention typically will be stable in the digestive system but are substantially hydrolyzed to the parental drug in the digestive lumen, liver or other metabolic organ, or within cells in general.

Exemplary Methods of Making the Compounds of the Invention.

The invention also relates to methods of making the compositions of the invention. The compositions are prepared by any of the applicable techniques of organic synthesis. Many such techniques are well known in the art. However, many of the known techniques are elaborated in Compendium of Organic Synthetic Methods (John Wiley & Sons, New York), Vol. 1, Ian T. Harrison and Shuyen Harrison, 1971; Vol. 2, Ian T. Harrison and Shuyen Harrison, 1974; Vol. 3, Louis S. Hegedus and Leroy Wade, 1977; Vol. 4, Leroy G. Wade, jr., 1980; Vol. 5, Leroy G. Wade, Jr., 1984; and Vol. 6, Michael B. Smith; as well as March, J., Advanced Organic Chemistry, Third Edition, (John Wiley & Sons, New York, 1985), Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes, Barry M. Trost, Editor-in-Chief (Pergamon Press, New York, 1993 printing).

A number of exemplary methods for the preparation of the compositions of the invention are provided below. These methods are intended to illustrate the nature of such preparations are not intended to limit the scope of applicable methods.

Generally, the reaction conditions such as temperature, reaction time, solvents, work-up procedures, and the like, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Work-up typically consists of quenching any unreacted reagents followed by partition between a water/organic layer system (extraction) and separating the layer containing the product.

Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20 °C), although for metal hydride reductions frequently the temperature is reduced to 0 °C to -100 °C, solvents are typically aprotic for reductions and may be either protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

Condensation reactions are typically carried out at temperatures near room temperature, although for non-equilibrating, kinetically controlled condensations reduced temperatures (0 °C to -100 °C) are also common. Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (*e.g.*, inert gas environments) are common in the art and will be applied when applicable.

Schemes and Examples

General aspects of these exemplary methods are described below and in the Examples. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

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Condensation reactions are typically carried out at temperatures near room temperature, although for non-equilibrating, kinetically controlled condensations reduced temperatures (0 °C to -100 °C) are also common. Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (*e.g.*, inert gas environments) are common in the art and will be applied when applicable.

The terms "treated", "treating", "treatment", and the like, when used in connection with a chemical synthetic operation, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with compound two" is synonymous with "allowing compound one to react with compound two", "contacting compound one with compound two", "reacting compound one with compound two", and other expressions common in the art of organic synthesis for reasonably indicating that compound one was "treated", "reacted", "allowed to react", etc., with compound two. For example, treating indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100 °C to 250 °C, typically -78 °C to 150 °C, more typically -78 °C to 100 °C, still more typically 0 °C to 100 °C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis are used in selecting the conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

Modifications of each of the exemplary schemes and in the examples (hereafter "exemplary schemes") leads to various analogs of the specific exemplary materials produce. The above-cited citations describing suitable methods of organic synthesis are applicable to such modifications.

In each of the exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium, and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

A single stereoisomer, *e.g.*, an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Stereochemistry of Carbon Compounds, (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) *J. Chromatogr.*, 113:(3) 283-302). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions.

Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α-methyl-β-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched xanthene. A method of determining optical purity involves making chiral esters, such as a menthyl ester, *e.g.*, (-) menthyl chloroformate in the presence of base, or Mosher ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob III. (1982) *J. Org. Chem.* 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase (Chiral Liquid Chromatography (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) *J. of Chromatogr.* 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

Examples General Section

A number of exemplary methods for the preparation of compounds of the invention are provided herein, for example, in the Examples hereinbelow.. These methods are intended to illustrate the nature of such preparations are not intended to limit the scope of applicable methods. Certain compounds of the invention can be used as intermediates for the preparation of other compounds of the invention. For example, the interconversion of various phosphonate compounds of the invention is illustrated below.

INTERCONVERSIONS OF THE PHOSPHONATES R-LINK-P(O)(OR^1)$_2$, R-LINK-P(O)(OR^1)(OH) AND R-LINK-P(O)(OH)$_2$.

The following schemes **32-38** described the preparation of phosphonate esters of the general structure R-link-P(O)(OR^1)$_2$, in which the groups R^1 may be the same or different. The R^1 groups attached to a phosphonate ester, or to precursors thereto, may be changed using established chemical transformations. The interconversion reactions of phosphonates are illustrated in Scheme **S32.** The group R in Scheme **32** represents the substructure, *i.e.* the drug "scaffold, to which the substituent link-P(O)(OR^1)$_2$ is attached, either in the compounds of the invention, or in precursors thereto. At the point in the synthetic route of conducting a phosphonate interconversion, certain functional groups in R may be protected. The methods employed for a given phosphonate transformation depend on the nature of the substituent R^1, and of the substrate to which the phosphonate group is attached. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

In general, synthesis of phosphonate esters is achieved by coupling a nucleophile amine or alcohol with the corresponding activated phosphonate electrophilic precursor. For example, chlorophosphonate addition on to 5'-hydroxy of nucleoside is a well known method for preparation of nucleoside phosphate monoesters. The activated precursor can be prepared by several well known methods. Chlorophosphonates useful for synthesis of the prodrugs are prepared from the substituted-1,3-propanediol (Wissner, et al, (1992) *J. Med Chem.* 35:1650). Chlorophosphonates are made by oxidation of the corresponding chlorophospholanes (Anderson, et al, (1984) *J. Org. Chem.* 49:1304) which are obtained by reaction of the substituted diol with phosphorus trichloride. Alternatively, the chlorophosphonate agent is made by treating substituted-1,3-diols with phosphorusoxychloride (Patois, et al, (1990) *J. Chem. Soc. Perkin Trans. I*, 1577). Chlorophosphonate species may also be generated in situ from corresponding cyclic phosphites (Silverburg, *et al.*, (1996) *Tetrahedron lett.*, 37:771-774), which in turn can be either made from chlorophospholane or phosphoramidate intermediate. Phosphoroflouridate intermediate prepared either from pyrophosphate or phosphoric acid may also act as precursor in preparation of cyclic prodrugs (Watanabe *et al.*, (1988) *Tetrahedron lett.*, 29:5763-66).

Phosphonate prodrugs of the present invention may also be prepared from the free acid by Mitsunobu reactions (Mitsunobu, (1981) *Synthesis*, 1; Campbell, (1992) *J. Org. Chem.* 57:6331), and other acid coupling reagents including, but not limited to, carbodiimides (Alexander, et al, (1994) *Collect. Czech. Chem. Commun.* 59:1853; Casara et al, (1992) *Bioorg. Med. Chem. Lett.* 2:145; Ohashi et al, (1988) *Tetrahedron Lett.*, 29:1189), and benzotriazolyloxytris-(dimethylamino)phosphonium salts (Campagne et al (1993) *Tetrahedron Lett.* 34:6743).

Aryl halides undergo Ni^{+2} catalyzed reaction with phosphite derivatives to give aryl phosphonate containing compounds (Balthazar, et al (1980) *J. Org. Chem.* 45:5425). Phosphonates may also be prepared from the chlorophosphonate in the presence of a palladium catalyst using aromatic triflates (Petrakis et al (1987) *J. Am. Chem. Soc.* 109:2831; Lu et al (1987) *Synthesis* 726). In another method, aryl phosphonate esters are prepared from aryl phosphates under anionic rearrangement conditions (Melvin (1981) *Tetrahedron Lett.* 22:3375; Casteel et al (1991) *Synthesis*, 691). N-Alkoxy aryl salts with alkali met al derivatives of cyclic alkyl phosphonate provide general synthesis for heteroaryl-2-phosphonate linkers (Redmore (1970) *J. Org. Chem.*

35:4114). These above mentioned methods can also be extended to compounds where the W^5 group is a heterocycle. Cyclic-1,3-propanyl prodrugs of phosphonates are also synthesized from phosphonic diacids and substituted propane-1,3-diols using a coupling reagent such as 1,3-dicyclohexylcarbodiimide (DCC) in presence of a base (*e.g.*, pyridine). Other carbodiimide based coupling agents like 1,3-disopropylcarbodiimide or water soluble reagent, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) can also be utilized for the synthesis of cyclic phosphonate prodrugs.

The conversion of a phosphonate diester **S32.1** into the corresponding phosphonate monoester **S32.2** (Scheme **32**, Reaction **1**) is accomplished by a number of methods. For example, the ester **S32.1** in which R^1 is an aralkyl group such as benzyl, is converted into the monoester compound **S32.2** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in *J. Org. Chem.* (1995) 60:2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110 °C. The conversion of the diester **S32.1** in which R^1 is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **S32.2** is effected by treatment of the ester **S32.1** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters **S32.1** in which one of the groups R^1 is aralkyl, such as benzyl, and the other is alkyl, is converted into the monoesters **S32.2** in which R^1 is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R^1 are alkenyl, such as allyl, is converted into the monoester **S32.2** in which R^1 is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in *J. Org. Chem.* (1973) 38:3224, for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **S32.1** or a phosphonate monoester **S32.2** into the corresponding phosphonic acid **S32.3** (Scheme **32**, Reactions **2** and **3**) can be effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in *J. Chem. Soc., Chem. Comm.*,

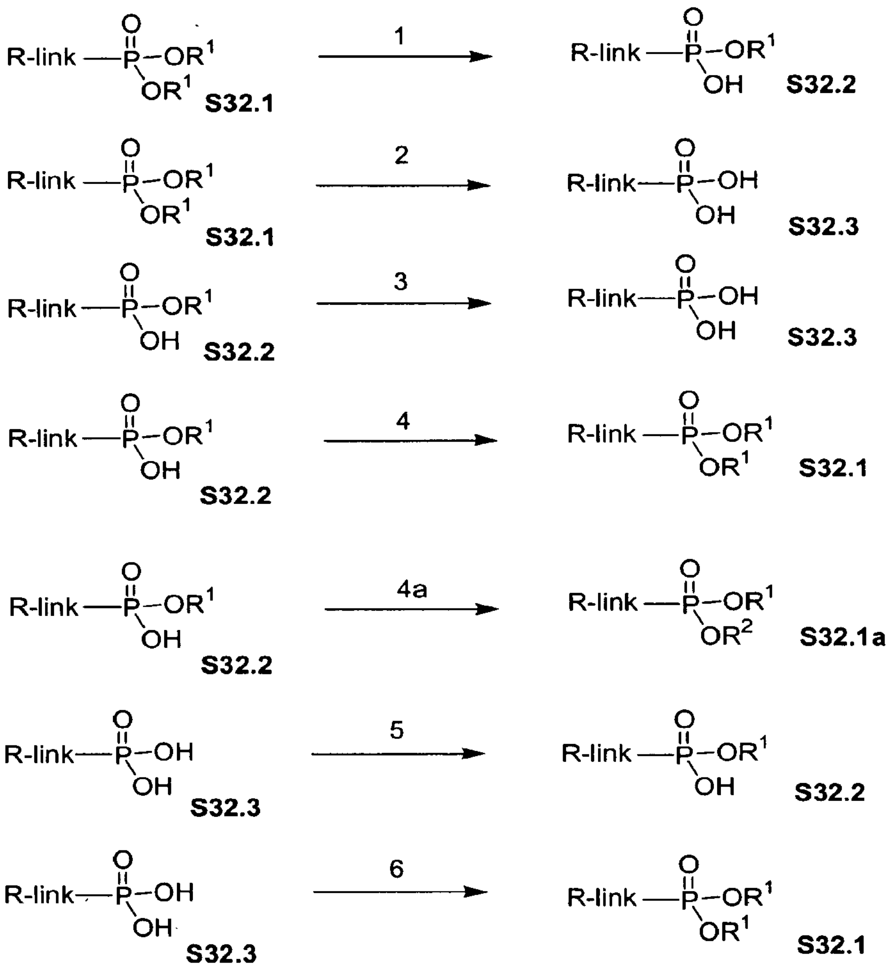
(1979) 739. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **S32.2** in which R^1 is aralkyl such as benzyl, is converted into the corresponding phosphonic acid **S32.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as dioxane. A phosphonate monoester **S32.2** in which R^1 is alkenyl such as, for example, allyl, is converted into the phosphonic acid **S32.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta.* (1985) 68:618. Palladium catalyzed hydrogenolysis of phosphonate esters **S32.1** in which R^1 is benzyl is described in *J. Org. Chem.* (1959) 24:434. Platinum-catalyzed hydrogenolysis of phosphonate esters **S32.1** in which R^1 is phenyl is described in *J. Am. Chem. Soc.* (1956) 78:2336.

The conversion of a phosphonate monoester **S32.2** into a phosphonate diester **S32.1** (Scheme **32**, Reaction **4**) in which the newly introduced R^1 group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl is effected by a number of reactions in which the substrate **S32.2** is reacted with a hydroxy compound R^1OH, in the presence of a coupling agent. Typically, the second phosphonate ester group is different than the first introduced phosphonate ester group, *i.e.* R^1 is followed by the introduction of R^2 where each of R^1 and R^2 is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl (Scheme **32**, Reaction **4a**) whereby **S32.2** is converted to **S32.1a**. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **S32.2** to the diester **S32.1** is effected by the use of the Mitsunobu reaction, as described above (Scheme **7**). The substrate is reacted with the hydroxy compound R^1OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **S32.2** is transformed into the phosphonate diester **S32.1**, in which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br, in which R^1 is as alkenyl or aralkyl. The alkylation reaction is conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester is transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **S32.2** is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH, in the presence of a base such as triethylamine, to afford the phosphonate diester **S32.1**.

A phosphonic acid R-link-$P(O)(OH)_2$ is transformed into a phosphonate monoester $RP(O)(OR^1)(OH)$ (Scheme **32**, Reaction **5**) by means of the methods described above of for the preparation of the phosphonate diester R-link-$P(O)(OR^1)_2$ **S32.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed. Dialkyl phosphonates may be prepared according to the methods of: Quast et al (1974) *Synthesis* 490; Stowell et al (1990) *Tetrahedron Lett.* 3261; US 5663159.

A phosphonic acid R-link-$P(O)(OH)_2$ **S32.3** is transformed into a phosphonate diester R-link-$P(O)(OR^1)_2$ **S32.1** (Scheme **32**, Reaction **6**) by a coupling reaction with the hydroxy compound R^1OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **S32.3** are transformed into phosphonic esters **S32.1** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70 °C. Alternatively, phosphonic acids **S32.3** are transformed into phosphonic esters **S32.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **S32.1**.

Scheme 32



Preparation of phosphonate carbamates.

Phosphonate esters may contain a carbamate linkage. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff. The carbamoyl group may be formed by reaction of a hydroxy group according to the methods known in the art, including the teachings of Ellis, US 2002/0103378 A1 and Hajima, US 6018049.

Scheme **33** illustrates various methods by which the carbamate linkage is synthesized. As shown in Scheme **33**, in the general reaction generating carbamates, an alcohol **S33.1**, is converted into the activated derivative **S33.2** in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described herein. The activated derivative **S33.2** is then reacted with an amine **S33.3**, to afford the carbamate product **S33.4**. Examples **1** – **7** in Scheme **33** depict methods by which the general reaction is effected. Examples **8 - 10** illustrate alternative methods for the preparation of carbamates.

Scheme **33**, Example **1** illustrates the preparation of carbamates employing a chloroformyl derivative of the alcohol **S33.5**. In this procedure, the alcohol **S33.5** is reacted with phosgene, in an inert solvent such as toluene, at about 0 °C, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate **S33.6**. The latter compound is then reacted with the amine component **S33.3**, in the presence of an organic or inorganic base, to afford the carbamate **S33.7**. For example, the chloroformyl compound **S33.6** is reacted with the amine **S33.3** in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate **S33.7**. Alternatively, the reaction is performed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme **33**, Example **2** depicts the reaction of the chloroformate compound **S33.6** with imidazole to produce the imidazolide **S33.8**. The imidazolide product is then reacted with the amine **S33.3** to yield the carbamate **S33.7**. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in *J. Med. Chem.*, 1989, 32, 357.

Scheme **33** Example **3**, depicts the reaction of the chloroformate **S33.6** with an activated hydroxyl compound R''OH, to yield the mixed carbonate ester **S33.10**. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds **S33.19** - **S33.24** shown in Scheme **33**, and similar compounds. For example, if the component R"OH is hydroxybenztriazole **S33.19**, N-hydroxysuccinimide **S33.20**, or pentachlorophenol, **S33.21**, the mixed carbonate **S33.10** is obtained by the reaction of the chloroformate with the hydroxyl compound in an ethereal solvent in the presence of dicyclohexylamine, as described in *Can. J. Chem.*, 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol **S33.22** or 2-hydroxypyridine **S33.23** is performed in an ethereal solvent in the presence of triethylamine, as described in *Syn.*, 1986, 303, and *Chem. Ber.* 118, 468, 1985.

Scheme **33** Example **4** illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole **S33.8** is employed. In this procedure, an alcohol **S33.5** is reacted with an equimolar amount of carbonyl diimidazole **S33.11** to prepare the intermediate **S33.8**. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole **S33.8** is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **S33.7**. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in *Tet. Lett.*, 42, 2001, 5227, to afford the carbamate **S33.7**.

Scheme **33**, Example **5** illustrates the preparation of carbamates by means of an intermediate alkoxycarbonylbenztriazole **S33.13**. In this procedure, an alcohol ROH is reacted at ambient temperature with an equimolar amount of benztriazole carbonyl chloride **S33.12**, to afford the alkoxycarbonyl product **S33.13**. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in *Synthesis.*, 1977, 704. The product is then reacted with the amine $R'NH_2$ to afford the carbamate **S33.7**. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80 °C as described in *Synthesis.*, 1977, 704.

Scheme **33**, Example **6** illustrates the preparation of carbamates in which a carbonate (R"O)$_2$CO, **S33.14**, is reacted with an alcohol **S33.5** to afford the intermediate alkyloxycarbonyl intermediate **S33.15**. The latter reagent is then reacted with the amine R'NH$_2$ to afford the carbamate **S33.7**. The procedure in which the reagent **S33.15** is derived from hydroxybenztriazole **S33.19** is described in *Synthesis*, 1993, 908; the procedure in which the reagent **S33.15** is derived from N-hydroxysuccinimide **S33.20** is described in *Tet. Lett.*, 1992, 2781; the procedure in which the reagent **S33.15** is derived from 2-hydroxypyridine **S33.23** is described in *Tet. Lett.*, 1991, 4251; the procedure in which the reagent **S33.15** is derived from 4-nitrophenol **S33.24** is described in *Synthesis*. 1993, 103. The reaction between equimolar amounts of the alcohol ROH and the carbonate **S33.14** is conducted in an inert organic solvent at ambient temperature.

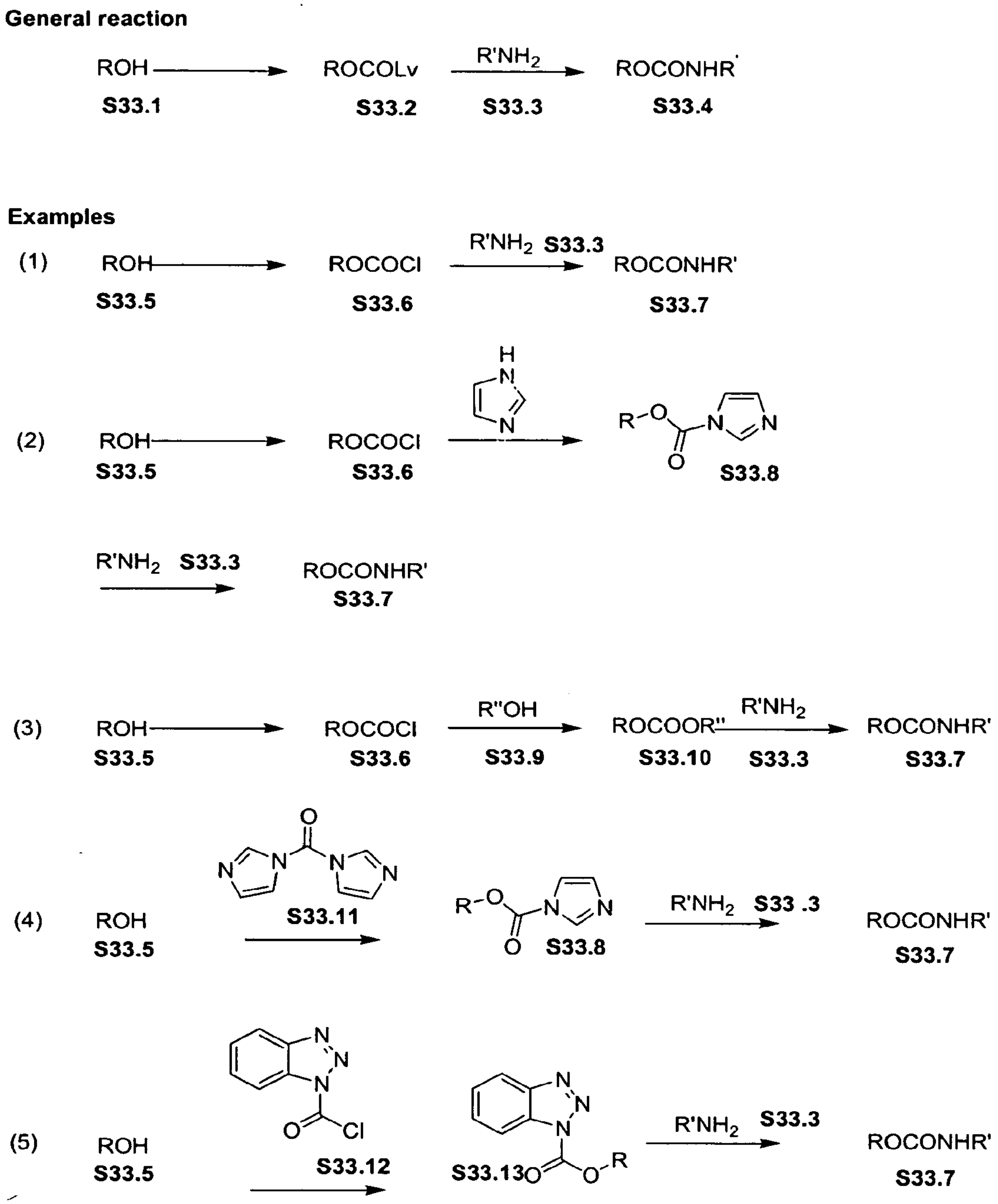
Scheme **33**, Example **7** illustrates the preparation of carbamates from alkoxycarbonyl azides **S33.16**. In this procedure, an alkyl chloroformate **S33.6** is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide **S33.16**. The latter compound is then reacted with an equimolar amount of the amine R'NH$_2$ to afford the carbamate **S33.7**. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in *Synthesis.*, 1982, 404.

Scheme **33**, Example **8** illustrates the preparation of carbamates by means of the reaction between an alcohol ROH and the chloroformyl derivative of an amine **S33.17**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate **S33.7**.

Scheme **33**, Example **9** illustrates the preparation of carbamates by means of the reaction between an alcohol ROH and an isocyanate **S33.18**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate **S33.7**.

Scheme **33**, Example **10** illustrates the preparation of carbamates by means of the reaction between an alcohol ROH and an amine R'NH_2. In this procedure, which is described in *Chem. Lett.* 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate **S33.7**.

Scheme 33. Preparation of carbamates.


General reaction
ROH
S33.1
ROCOLv
S33.2
R'NH2
S33.3
ROCONHR'
S33.4
Examples
(1)
ROH
S33.5
ROCOCl
S33.6
R'NH2 S33.3
ROCONHR'
S33.7
(2)
ROH
S33.5
ROCOCl
S33.6
H
N
N
R
O
O
N
N
S33.8
R'NH2 S33.3
ROCONHR'
S33.7
(3)
ROH
S33.5
ROCOCl
S33.6
R"OH
S33.9
ROCOOR"
S33.10
R'NH2
S33.3
ROCONHR'
S33.7
(4)
ROH
S33.5
O
N
N
N
N
S33.11
R
O
O
N
N
S33.8
R'NH2 S33.3
ROCONHR'
S33.7
(5)
ROH
S33.5
N
N
N
O
Cl
S33.12
N
N
N
S33.13
O
O
R
R'NH2 S33.3
ROCONHR'
S33.7

(6) $\underset{\textbf{S33.5}}{\text{ROH}} \xrightarrow[\textbf{S33.14}]{\text{(R''O}_2\text{)C=O}} \underset{\textbf{S33.15}}{\text{ROCOR''}} \xrightarrow[\textbf{S33.3}]{\text{R'NH}_2} \underset{\textbf{S33.7}}{\text{ROCONHR'}}$

(7) $\underset{\textbf{S33.5}}{\text{ROH}} \longrightarrow \underset{\textbf{S33.6}}{\text{ROCOCl}} \longrightarrow \underset{\textbf{S33.16}}{\text{ROCON}_3}$

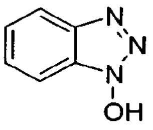
$\xrightarrow{\text{R'NH}_2\ \textbf{33.3}} \underset{\textbf{33.7}}{\text{ROCONHR'}}$

(8) $\underset{\textbf{S33.5}}{\text{ROH}} \xrightarrow[\textbf{S33.17}]{\text{R'NHCOCl}} \underset{\textbf{S33.7}}{\text{ROCONHR'}}$

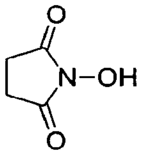
(9) $\underset{\textbf{S33.5}}{\text{ROH}} \xrightarrow[\textbf{S33.18}]{\text{R'NCO}} \underset{\textbf{S33.7}}{\text{ROCONHR'}}$

(10) $\underset{\textbf{S33.5}}{\text{ROH}} \xrightarrow[\textbf{S33.3}]{\text{R'NH}_2} \underset{\textbf{S33.7}}{\text{ROCONHR'}}$

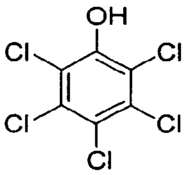
R"OH =



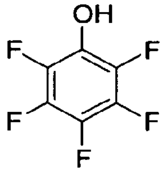
S33.19



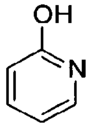
S33.20



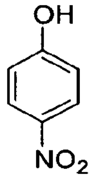
S33.21



S33.22



S33.23



S33.24

PREPARATION OF CARBOALKOXY-SUBSTITUTED PHOSPHONATE BISAMIDATES, MONOAMIDATES, DIESTERS AND MONOESTERS.

A number of methods are available for the conversion of phosphonic acids into amidates and esters. In one group of methods, the phosphonic acid is either converted into an isolated activated intermediate such as a phosphoryl chloride, or the phosphonic acid is activated in situ for reaction with an amine or a hydroxy compound.

The conversion of phosphonic acids into phosphoryl chlorides is accomplished by reaction with thionyl chloride, for example as described in *J. Gen. Chem. USSR*, 1983, 53, 480, *Zh. Obschei Khim.*, 1958, 28, 1063, or *J. Org. Chem.*, 1994, 59, 6144, or by reaction with oxalyl chloride, as described in *J. Am. Chem. Soc.*, 1994, 116, 3251, or *J. Org. Chem.*, 1994, 59, 6144, or by reaction with phosphorus pentachloride, as described in *J. Org. Chem.*, 2001, 66, 329, or in *J. Med. Chem.*, 1995, 38, 1372. The resultant phosphoryl chlorides are then reacted with amines or hydroxy compounds in the presence of a base to afford the amidate or ester products.

Phosphonic acids are converted into activated imidazolyl derivatives by reaction with carbonyl diimidazole, as described in *J. Chem. Soc., Chem. Comm.* (1991) 312, or *Nucleosides & Nucleotides* (2000) 19:1885. Activated sulfonyloxy derivatives are obtained by the reaction of phosphonic acids with trichloromethylsulfonyl chloride or with triisopropylbenzenesulfonyl chloride, as described in *Tet. Lett.* (1996) 7857, or *Bioorg. Med. Chem. Lett.* (1998) 8:663. The activated sulfonyloxy derivatives are then reacted with amines or hydroxy compounds to afford amidates or esters.

Alternatively, the phosphonic acid and the amine or hydroxy reactant are combined in the presence of a diimide coupling agent. The preparation of phosphonic amidates and esters by means of coupling reactions in the presence of dicyclohexyl carbodiimide is described, for example, in *J. Chem. Soc., Chem. Comm.* (1991) 312 or *Coll. Czech. Chem. Comm.* (1987) 52:2792. The use of ethyl dimethylaminopropyl carbodiimide for activation and coupling of phosphonic acids is described in *Tet. Lett.*, (2001) 42:8841, or *Nucleosides & Nucleotides* (2000) 19:1885.

A number of additional coupling reagents have been described for the preparation of amidates and esters from phosphonic acids. The agents include Aldrithiol-2, and PYBOP and BOP, as described in *J. Org. Chem.*, 1995, 60, 5214, and *J. Med. Chem.* (1997) 40:3842, mesitylene-2-sulfonyl-3-nitro-1,2,4-

triazole (MSNT), as described in *J. Med. Chem.* (1996) 39:4958, diphenylphosphoryl azide, as described in *J. Org. Chem.* (1984) 49:1158, 1-(2,4,6-triisopropylbenzenesulfonyl-3-nitro-1,2,4-triazole (TPSNT) as described in *Bioorg. Med. Chem. Lett.* (1998) 8:1013, bromotris(dimethylamino)phosphonium hexafluorophosphate (BroP), as described in *Tet. Lett.*, (1996) 37:3997, 2-chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphinane, as described in *Nucleosides Nucleotides* 1995, 14, 871, and diphenyl chlorophosphate, as described in *J. Med. Chem.*, 1988, 31, 1305.

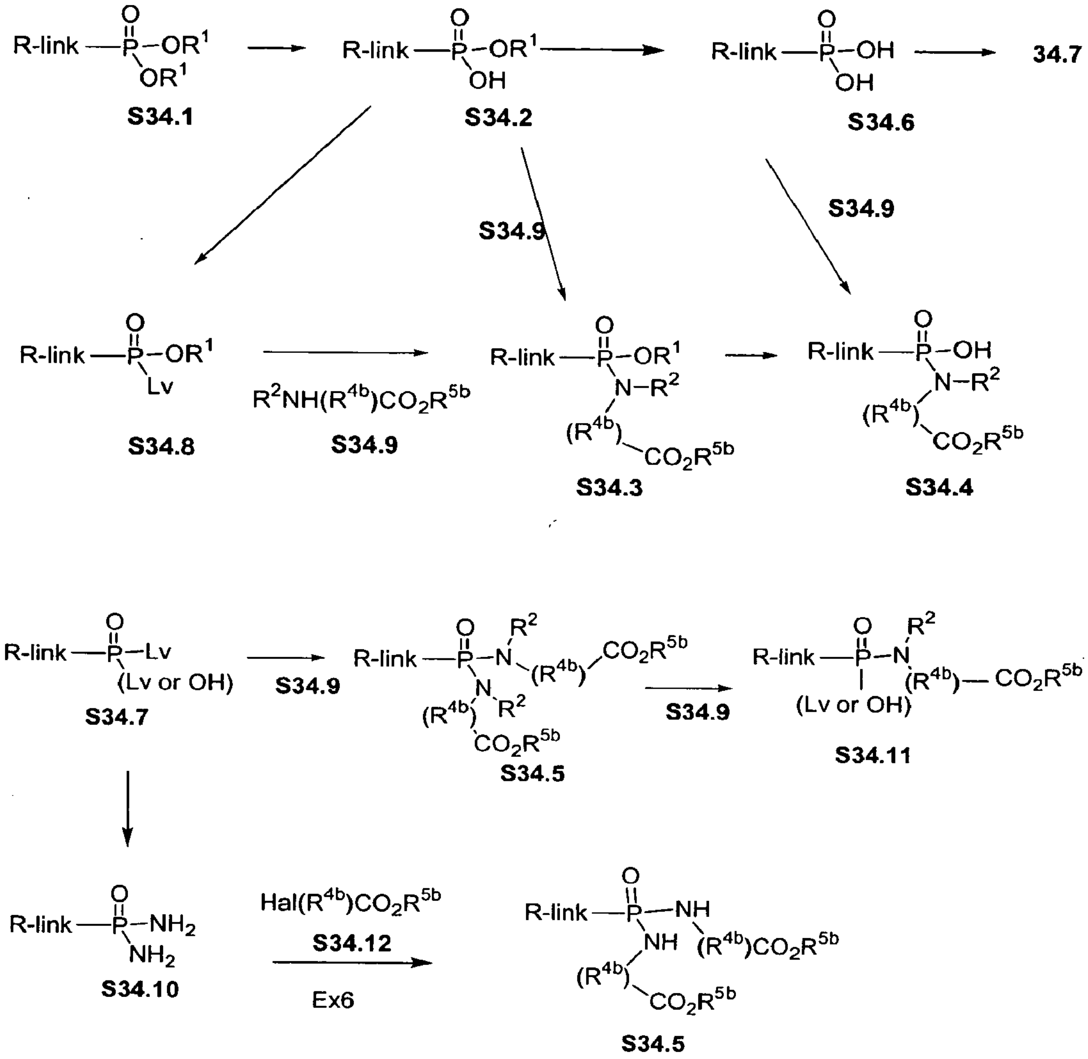
Phosphonic acids are converted into amidates and esters by means of the Mitsunobu reaction, in which the phosphonic acid and the amine or hydroxy reactant are combined in the presence of a triaryl phosphine and a dialkyl azodicarboxylate. The procedure is described in *Org. Lett.*, 2001, 3, 643, or *J. Med. Chem.*, 1997, 40, 3842.

Phosphonic esters are also obtained by the reaction between phosphonic acids and halo compounds, in the presence of a suitable base. The method is described, for example, in *Anal. Chem.*, 1987, 59, 1056, or *J. Chem. Soc. Perkin Trans., I*, 1993, 19, 2303, or *J. Med. Chem.*, 1995, 38, 1372, or *Tet. Lett.*, 2002, 43, 1161.

Schemes **34-37** illustrate the conversion of phosphonate esters and phosphonic acids into carboalkoxy-substituted phosphonbisamidates (Scheme **34**), phosphonamidates (Scheme **35**), phosphonate monoesters (Scheme **36**) and phosphonate diesters, (Scheme **37**). Scheme 38 illustrates synthesis of gem-dialkyl amino phosphonate reagents.

Scheme **34** illustrates various methods for the conversion of phosphonate diesters **S34.1** into phosphonbisamidates **S34.5**. The diester **S34.1**, prepared as described previously, is hydrolyzed, either to the monoester **S34.2** or to the phosphonic acid **S34.6**. The methods employed for these transformations are described above. The monoester **S34.2** is converted into the monoamidate **S34.3** by reaction with an aminoester **S34.9**, in which the group R^2 is H or alkyl; the group R^{4b} is a divalent alkylene moiety such as, for example, $CHCH_3$, $CHCH_2CH_3$, $CH(CH(CH_3)_2)$, $CH(CH_2Ph)$, and the like, or a side chain group present in natural or modified aminoacids; and the group R^{5b} is C_1–C_{12} alkyl, such as methyl, ethyl, propyl, isopropyl, or isobutyl; C_6–C_{20} aryl, such as phenyl or substituted phenyl; or C_6–C_{20} arylalkyl, such as benzyl or benzyhydryl. The reactants are combined in the presence of a coupling agent such as a carbodiimide, for example dicyclohexyl carbodiimide, as described in *J. Am. Chem. Soc.*, (1957) 79:3575, optionally in the presence of an activating agent such as hydroxybenztriazole, to yield the amidate product **S34.3**. The amidate-forming reaction is also effected in the presence of coupling agents such as BOP, as described in *J. Org. Chem.* (1995) 60:5214, Aldrithiol, PYBOP and similar coupling agents used for the preparation of amides and esters. Alternatively, the reactants **S34.2** and **S34.9** are transformed into the monoamidate **S34.3** by means of a Mitsunobu reaction. The preparation of amidates by means of the Mitsunobu reaction is described in *J. Med. Chem.* (1995) 38:2742. Equimolar amounts of the reactants are combined in an inert solvent such as tetrahydrofuran in the presence of a triaryl phosphine and a dialkyl azodicarboxylate. The thus-obtained monoamidate ester **S34.3** is then transformed into amidate phosphonic acid **S34.4**. The conditions used for the hydrolysis reaction depend on the nature of the R^1 group, as described previously. The phosphonic acid amidate **S34.4** is then reacted with an aminoester **S34.9**, as described above, to yield the bisamidate product **S34.5**, in which the amino substituents are the same or different. Alternatively, the phosphonic acid **S34.6** may be treated with two different amino ester reagents simulataneously, *i.e.* **S34.9** where R^2, R^{4b} or R^{5b} are different. The resulting mixture of bisamidate products **S34.5** may then be separable, *e.g.*, by chromatography.

Scheme 34


R-link—P(=O)(OR1)OR1
S34.1
R-link—P(=O)(OR1)OH
S34.2
R-link—P(=O)(OH)OH
S34.6
34.7
S34.9
S34.9
R-link—P(=O)(OR1)Lv
S34.8
R2NH(R4b)CO2R5b
S34.9
R-link—P(=O)(OR1)N-R2 (R4b)CO2R5b
S34.3
R-link—P(=O)(OH)N-R2 (R4b)CO2R5b
S34.4
R-link—P(=O)Lv (Lv or OH)
S34.7
S34.9
S34.5
S34.9
(Lv or OH)
S34.11
R-link—P(=O)(NH2)NH2
S34.10
Hal(R4b)CO2R5b
S34.12
Ex6
S34.5

An example of this procedure is shown in Scheme **34**, Example **1**. In this procedure, a dibenzyl phosphonate **S34.14** is reacted with diazabicyclooctane (DABCO) in toluene at reflux, as described in *J. Org. Chem.*, 1995, 60, 2946, to afford the monobenzyl phosphonate **S34.15**. The product is then reacted with equimolar amounts of ethyl alaninate **S34.16** and dicyclohexyl carbodiimide in pyridine, to yield the amidate product S34.17. The benzyl group is then removed, for example by hydrogenolysis over a palladium catalyst, to give the monoacid product **S34.18** which may be unstable according to J. Med. Chem. (1997) 40(23):3842. This compound **S34.18** is then reacted in a Mitsunobu reaction with ethyl leucinate **S34.19**, triphenyl phosphine and diethylazodicarboxylate, as described in *J. Med. Chem.*, 1995, 38, 2742, to produce the bisamidate product **S34.20**.

Using the above procedures, but employing in place of ethyl leucinate **S34.19** or ethyl alaninate **S34.16**, different aminoesters **S34.9**, the corresponding products **S34.5** are obtained.

Alternatively, the phosphonic acid **S34.6** is converted into the bisamidate **S34.5** by use of the coupling reactions described above. The reaction is performed in one step, in which case the nitrogen-related substituents present in the product **S34.5** are the same, or in two steps, in which case the nitrogen-related substituents can be different.

An example of the method is shown in Scheme 34, Example 2. In this procedure, a phosphonic acid **S34.6** is reacted in pyridine solution with excess ethyl phenylalaninate **S34.21** and dicyclohexylcarbodiimide, for example as described in *J. Chem. Soc., Chem. Comm.*, 1991, 1063, to give the bisamidate product **S34.22**.

Using the above procedures, but employing, in place of ethyl phenylalaninate, different aminoesters **S34.9**, the corresponding products **S34.5** are obtained.

As a further alternative, the phosphonic acid **S34.6** is converted into the mono or bis-activated derivative **S34.7**, in which Lv is a leaving group such as chloro, imidazolyl, triisopropylbenzenesulfonyloxy etc. The conversion of phosphonic acids into chlorides **S34.7** (Lv = Cl) is effected by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17. The conversion of phosphonic acids into monoimidazolides **S34.7** (Lv = imidazolyl) is described in *J. Med. Chem.*, 2002, 45, 1284 and in *J. Chem. Soc. Chem. Comm.*, 1991, 312. Alternatively, the phosphonic acid is activated by reaction with triisopropylbenzenesulfonyl chloride, as described in *Nucleosides and Nucleotides*, 2000, 10, 1885. The activated product is then reacted with the aminoester **S34.9**, in the presence of a base, to give the bisamidate **S34.5**. The reaction is performed in one step, in which case the nitrogen substituents present in the product **S34.5** are the same, or in two steps, via the intermediate **S34.11**, in which case the nitrogen substituents can be different.

Examples of these methods are shown in Scheme 34, Examples 3 and 5. In the procedure illustrated in Scheme 34, Example 3, a phosphonic acid **S34.6** is reacted with ten molar equivalents of thionyl chloride, as described in *Zh. Obschei Khim.*, 1958, 28, 1063, to give the dichloro compound **S34.23**. The product is then reacted at reflux temperature in a polar aprotic solvent such as acetonitrile, and in the presence of a base such as triethylamine, with butyl serinate **S34.24** to afford the bisamidate product **S34.25**.

Using the above procedures, but employing, in place of butyl serinate **S34.24**, different aminoesters **S34.9**, the corresponding products **S34.5** are obtained.

In the procedure illustrated in Scheme 34, Example 5, the phosphonic acid **S34.6** is reacted, as described in *J. Chem. Soc. Chem. Comm.*, 1991, 312, with carbonyl diimidazole to give the imidazolide **S34.32.** The product is then reacted in acetonitrile solution at ambient temperature, with one molar equivalent of ethyl alaninate **S34.33** to yield the monodisplacement product **S34.34.** The latter compound is then reacted with carbonyl diimidazole to produce the activated intermediate **S34.35**, and the product is then reacted, under the same conditions, with ethyl N-methylalaninate **S34.33a** to give the bisamidate product **S34.36**.

Using the above procedures, but employing, in place of ethyl alaninate **S34.33** or ethyl N-methylalaninate **S34.33a**, different aminoesters **S34.9**, the corresponding products **S34.5** are obtained.

The intermediate monoamidate **S34.3** is also prepared from the monoester **S34.2** by first converting the monoester into the activated derivative **S34.8** in which Lv is a leaving group such as halo, imidazolyl etc, using the procedures described above. The product **S34.8** is then reacted with an aminoester **S34.9** in the presence of a base such as pyridine, to give an intermediate monoamidate product **S34.3**. The latter compound is then converted, by removal of the R^1 group and coupling of the product with the aminoester **S34.9**, as described above, into the bisamidate **S34.5**.

An example of this procedure, in which the phosphonic acid is activated by conversion to the chloro derivative **S34.26**, is shown in Scheme 34, Example 4. In this procedure, the phosphonic monobenzyl ester **S34.15** is reacted, in dichloromethane, with thionyl chloride, as described in *Tet. Letters.*, 1994, 35, 4097, to afford the phosphoryl chloride **S34.26**. The product is then reacted in acetonitrile solution at ambient temperature with one molar equivalent of ethyl 3-amino-2-methylpropionate **S34.27** to yield the monoamidate product **S34.28**. The latter compound is hydrogenated in ethylacetate over a 5% palladium on carbon catalyst to produce the monoacid product **S34.29**. The product is subjected to a Mitsunobu coupling procedure, with equimolar amounts of butyl alaninate **S34.30**, triphenyl phosphine, diethylazodicarboxylate and triethylamine in tetrahydrofuran, to give the bisamidate product **S34.31**.

Using the above procedures, but employing, in place of ethyl 3-amino-2-methylpropionate **S34.27** or butyl alaninate **S34.30**, different aminoesters **S34.9**, the corresponding products **S34.5** are obtained.

The activated phosphonic acid derivative **S34.7** is also converted into the bisamidate **S34.5** via the diamino compound **S34.10**. The conversion of activated phosphonic acid derivatives such as phosphoryl chlorides into the corresponding amino analogs **S34.10**, by reaction with ammonia, is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976. The bisamino compound **S34.10** is then reacted at elevated temperature with a haloester **S34.12** (Hal = halogen, *i.e.* F, Cl, Br, I), in a polar organic solvent such as dimethylformamide, in the presence of a base such as 4, 4-dimethylaminopyridine (DMAP) or potassium carbonate, to yield the bisamidate **S34.5**. Alternatively, **S34.6** may be treated with two different amino ester reagents simulataneously, *i.e.* **S34.12** where R^{4b} or R^{5b} are different. The resulting mixture of bisamidate products **S34.5** may then be separable, *e.g.*, by chromatography.

An example of this procedure is shown in Scheme 34, Example 6. In this method, a dichlorophosphonate **S34.23** is reacted with ammonia to afford the diamide **S34.37**. The reaction is performed in aqueous, aqueous alcoholic or alcoholic solution, at reflux temperature. The resulting diamino compound is then reacted with two molar equivalents of ethyl 2-bromo-3-methylbutyrate **S34.38**, in a polar organic solvent such as N-methylpyrrolidinone at ca. 150 °C, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, to afford the bisamidate product **S34.39**.

Using the above procedures, but employing, in place of ethyl 2-bromo-3-methylbutyrate **S34.38**, different haloesters **S34.12** the corresponding products **S34.5** are obtained.

The procedures shown in Scheme 34 are also applicable to the preparation of bisamidates in which the aminoester moiety incorporates different functional groups. Scheme 34, Example **7** illustrates the preparation of bisamidates derived from tyrosine. In this procedure, the monoimidazolide **S34.32** is reacted with propyl tyrosinate **S34.40**, as described in Example **5**, to yield the monoamidate **S34.41**. The product is reacted with carbonyl diimidazole to give the imidazolide **S34.42**, and this material is reacted with a further molar equivalent of propyl tyrosinate to produce the bisamidate product **S34.43**.

Using the above procedures, but employing, in place of propyl tyrosinate **S34.40**, different aminoesters **S34.9**, the corresponding products **S34.5** are obtained. The aminoesters employed in the two stages of the above procedure can be the same or different, so that bisamidates with the same or different amino substituents are prepared.

Scheme 35 illustrates methods for the preparation of phosphonate monoamidates.

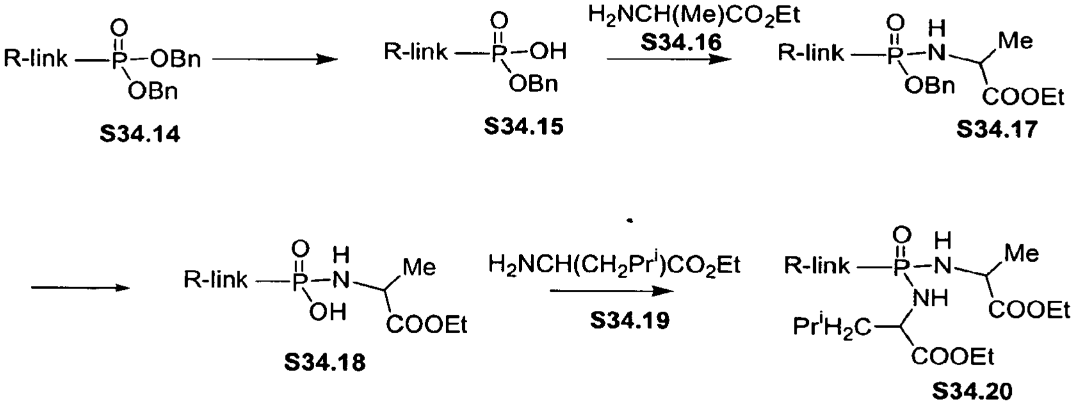
In one procedure, a phosphonate monoester **S34.1** is converted, as described in Scheme 34, into the activated derivative **S34.8**. This compound is then reacted, as described above, with an aminoester **S34.9**, in the presence of a base, to afford the monoamidate product **S35.1**.

The procedure is illustrated in Scheme 35, Example 1. In this method, a monophenyl phosphonate **S35.7** is reacted with, for example, thionyl chloride, as described in *J. Gen. Chem.* USSR., 1983, 32, 367, to give the chloro product **S35.8**. The product is then reacted, as described in Scheme 34, with ethyl alaninate, to yield the amidate **S35.10**.

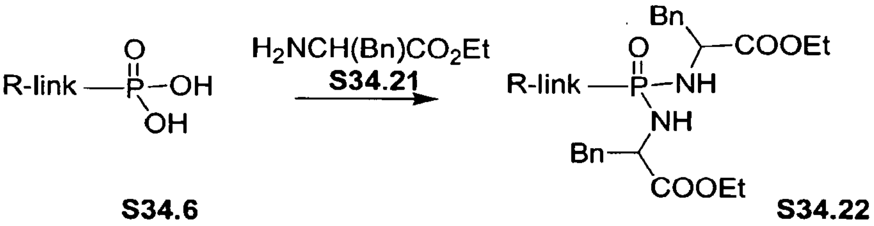
Using the above procedures, but employing, in place of ethyl alaninate **S35.9**, different aminoesters **S34.9**, the corresponding products **S35.1** are obtained.

Alternatively, the phosphonate monoester **S34.1** is coupled, as described in Scheme 34, with an aminoester **S34.9** to produce the amidate **S35.1**. If necessary, the R^1 substituent is then altered, by initial cleavage to afford the phosphonic acid **S35.2**. The procedures for this transformation depend on the nature of the R^1 group, and are described above. The phosphonic acid is then transformed into the ester amidate product **S35.3**, by reaction with the hydroxy compound R^3OH, in which the group R^3 is aryl, heterocycle, alkyl, cycloalkyl, haloalkyl etc, using the same coupling procedures (carbodiimide, Aldrithiol-2, PYBOP, Mitsunobu reaction etc) described in Scheme 34 for the coupling of amines and phosphonic acids.

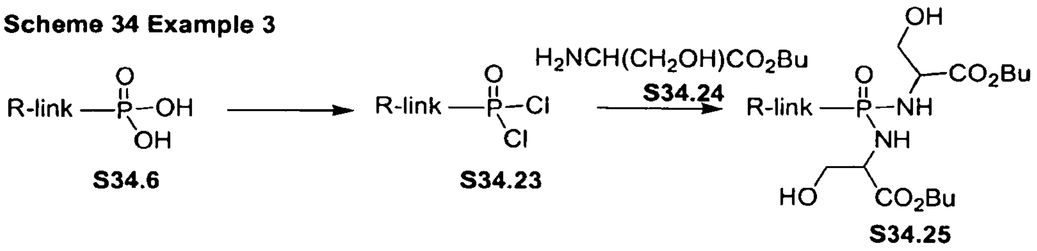
Scheme 34 Example 1


R-link
OBn
S34.14
S34.15
H2NCH(Me)CO2Et
S34.16
S34.17
Me
COOEt
S34.18
H2NCH(CH2Pri)CO2Et
S34.19
PriH2C
S34.20

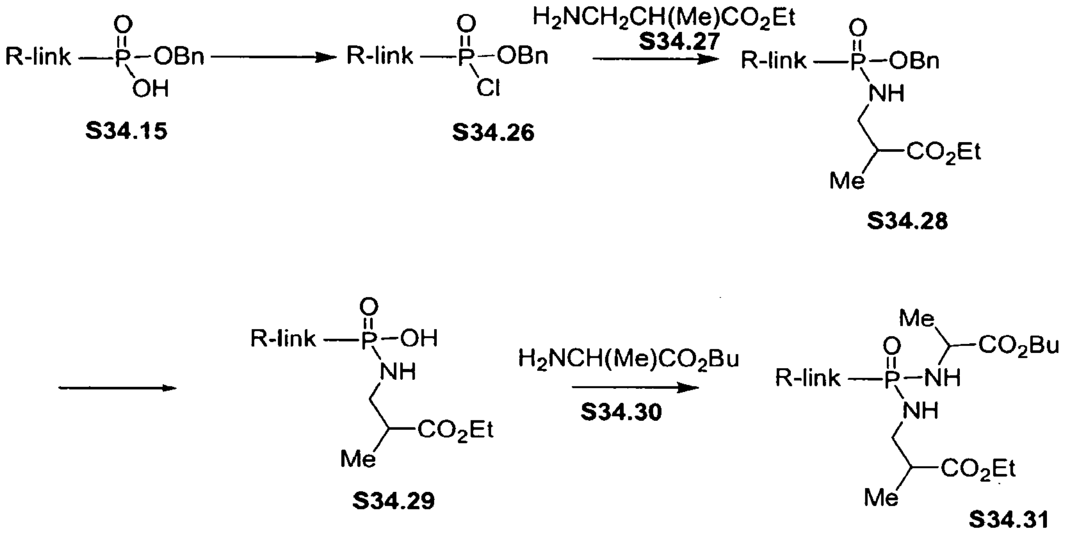
Scheme 34 Example 2


R-link
OH
S34.6
H2NCH(Bn)CO2Et
S34.21
Bn
COOEt
NH
S34.22

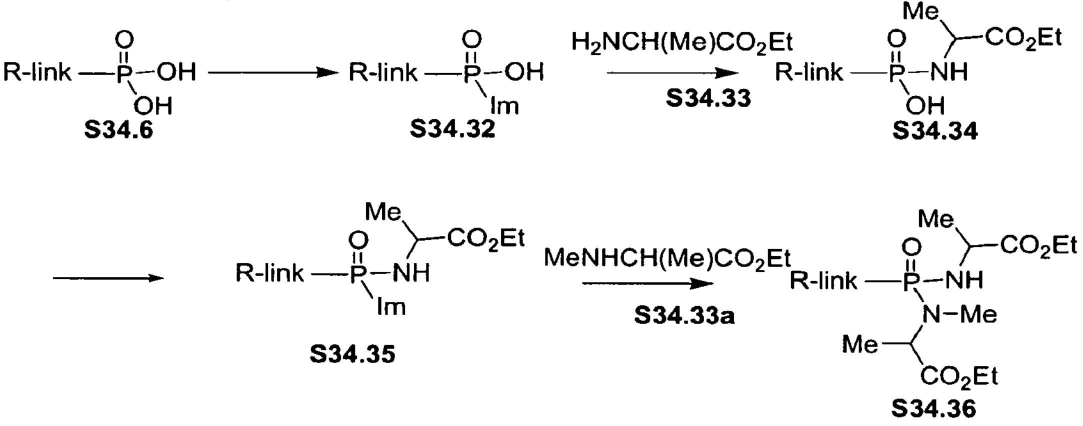
Scheme 34 Example 3


S34.6
S34.23
H2NCH(CH2OH)CO2Bu
S34.24
S34.25

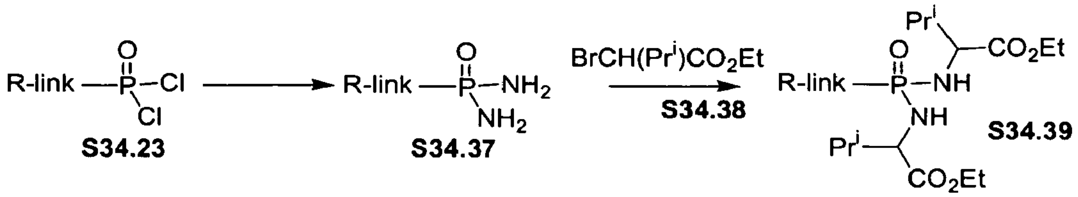
Scheme 34 Example 4


S34.15
S34.26
H2NCH2CH(Me)CO2Et
S34.27
S34.28
S34.29
H2NCH(Me)CO2Bu
S34.30
S34.31

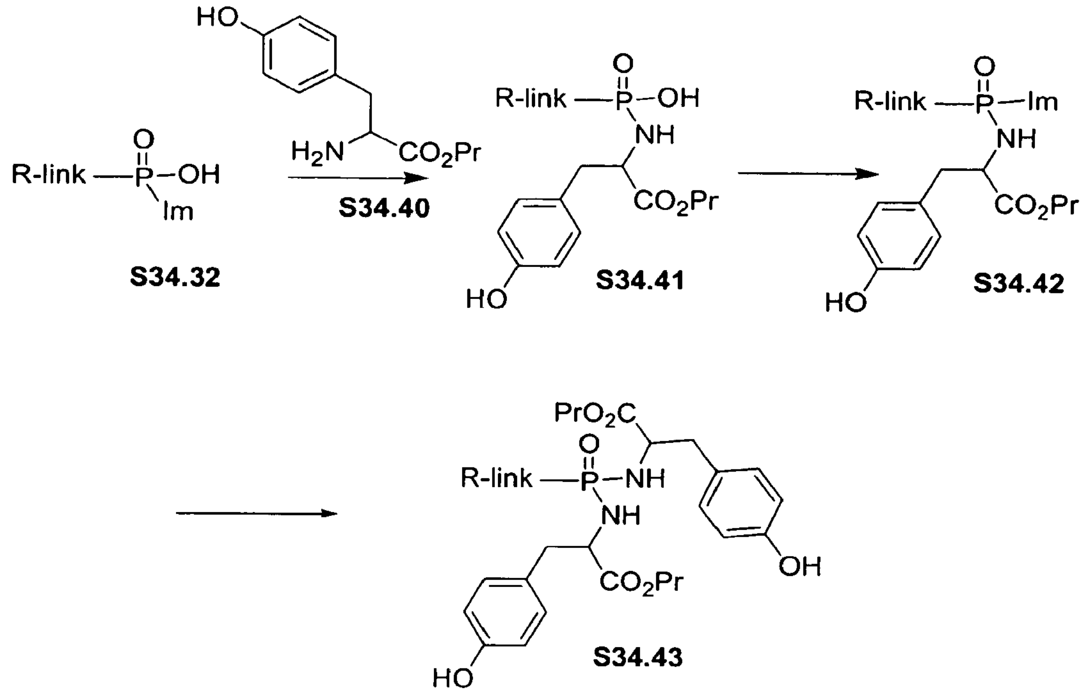
Scheme 34 Example 5


S34.6
S34.32
H2NCH(Me)CO2Et
S34.33
S34.34
S34.35
MeNHCH(Me)CO2Et
S34.33a
S34.36

Scheme 34 Example 6


S34.23
S34.37
BrCH(Pri)CO2Et
S34.38
S34.39

Scheme 34 Example 7



Examples of this method are shown in Scheme 35, Examples 1-3. In the sequence shown in Example 2, a monobenzyl phosphonate **S35.11** is transformed by reaction with ethyl alaninate, using one of the methods described above, into the monoamidate **S35.12**. The benzyl group is then removed by catalytic hydrogenation in ethylacetate solution over a 5% palladium on carbon catalyst, to afford the phosphonic acid amidate **S35.13**. The product is then reacted in dichloromethane solution at ambient temperature with equimolar amounts of 1-(dimethylaminopropyl)-3-ethylcarbodiimide and trifluoroethanol **S35.14**, for example as described in *Tet. Lett.*, 2001, 42, 8841, to yield the amidate ester **S35.15**.

In the sequence shown in Scheme 35, Example 3, the monoamidate **S35.13** is coupled, in tetrahydrofuran solution at ambient temperature, with equimolar amounts of dicyclohexyl carbodiimide and 4-hydroxy-N-methylpiperidine **S35.16**, to produce the amidate ester product **S35.17**.

Using the above procedures, but employing, in place of the ethyl alaninate product **S35.12** different monoacids **S35.2**, and in place of trifluoroethanol **S35.14** or 4-hydroxy-N-methylpiperidine **S35.16**, different hydroxy compounds R^3OH, the corresponding products **S35.3** are obtained.

Alternatively, the activated phosphonate ester **S34.8** is reacted with ammonia to yield the amidate **S35.4**. The product is then reacted, as described in Scheme 34, with a haloester **S35.5**, in the presence of a base, to produce the amidate product **S35.6**. If appropriate, the nature of the R^1 group is changed, using the procedures described above, to give the product **S35.3**. The method is illustrated in Scheme 35, Example **4**. In this sequence, the monophenyl phosphoryl chloride **S35.18** is reacted, as described in Scheme **34**, with ammonia, to yield the amino product **S35.19**. This material is then reacted in N-methylpyrrolidinone solution at 170° with butyl 2-bromo-3-phenylpropionate **S35.20** and potassium carbonate, to afford the amidate product **S35.21**.

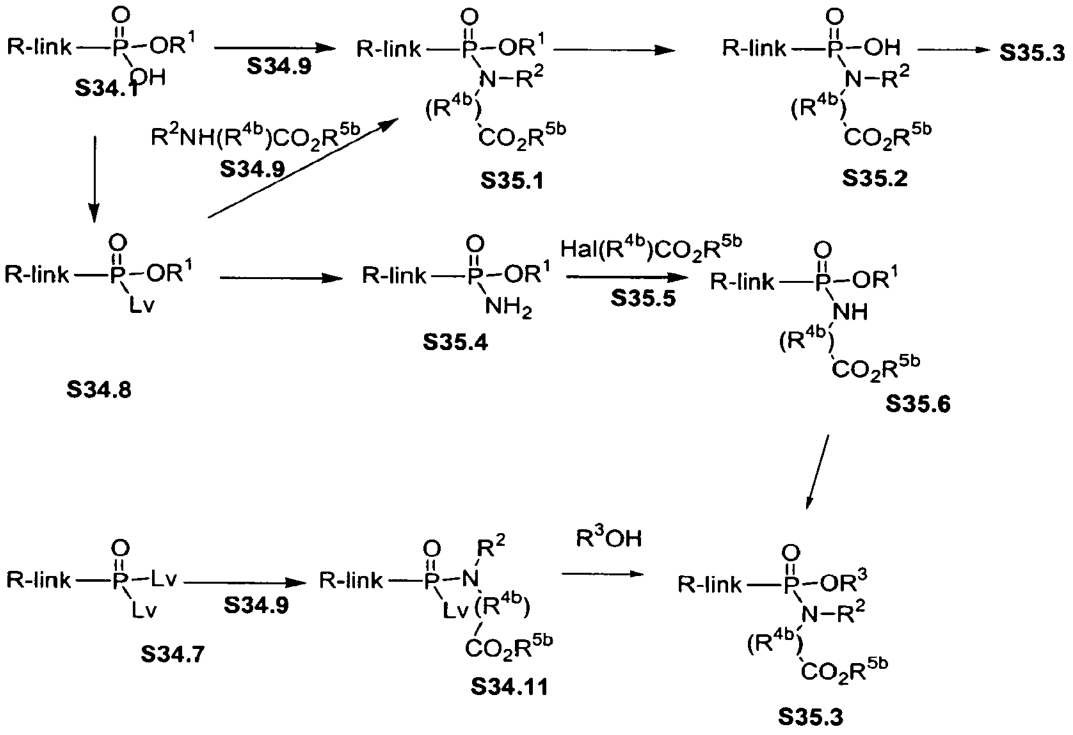
Using these procedures, but employing, in place of butyl 2-bromo-3-phenylpropionate **S35.20**, different haloesters **S35.5**, the corresponding products **S35.6** are obtained.

The monoamidate products **S35.3** are also prepared from the doubly activated phosphonate derivatives **S34.7**. In this procedure, examples of which are described in *Synlett.*, 1998, 1, 73, the intermediate **S34.7** is reacted with a limited amount of the aminoester **S34.9** to give the mono-displacement product **S34.11**. The latter compound is then reacted with the hydroxy compound R^3OH in a polar organic solvent such as dimethylformamide, in the presence of a base such as diisopropylethylamine, to yield the monoamidate ester **S35.3**.

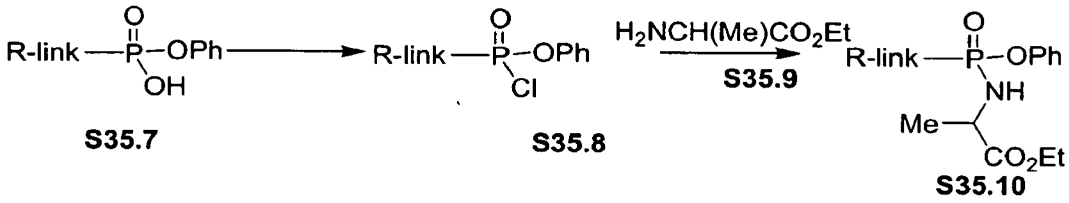
The method is illustrated in Scheme 35, Example 5. In this method, the phosphoryl dichloride **S35.22** is reacted in dichloromethane solution with one molar equivalent of ethyl N-methyl tyrosinate **S35.23** and dimethylaminopyridine, to generate the monoamidate **S35.24**. The product is then reacted with phenol **S35.25** in dimethylformamide containing potassium carbonate, to yield the ester amidate product **S35.26**.

Using these procedures, but employing, in place of ethyl N-methyl tyrosinate **S35.23** or phenol **S35.25**, the aminoesters **S34.9** and/or the hydroxy compounds R^3OH, the corresponding products **S35.3** are obtained.

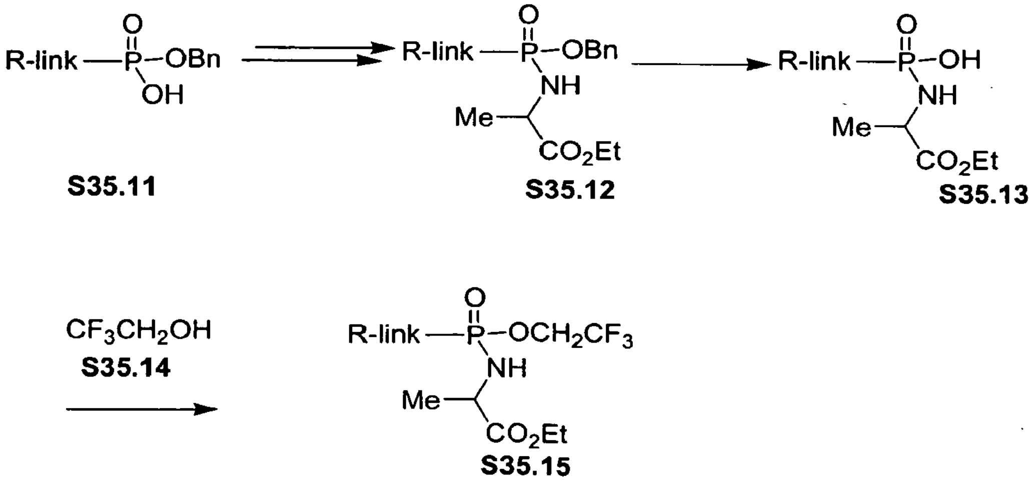
Scheme 35


R-link—P(O)(OR^1)OH
S34.1
S34.9
R^{2}NH(R^{4b})CO$_2$R^{5b}
S34.9
R-link—P(O)(OR^1)N(R^2)(R^{4b})CO$_2$R^{5b}
S35.1
R-link—P(O)(OH)N(R^2)(R^{4b})CO$_2$R^{5b}
S35.2
S35.3
R-link—P(O)(OR^1)Lv
S34.8
R-link—P(O)(OR^1)NH$_2$
S35.4
Hal(R^{4b})CO$_2$R^{5b}
S35.5
R-link—P(O)(OR^1)NH(R^{4b})CO$_2$R^{5b}
S35.6
R-link—P(O)(Lv)Lv
S34.7
S34.9
R-link—P(O)(Lv)N(R^2)(R^{4b})CO$_2$R^{5b}
S34.11
R^{3}OH
R-link—P(O)(OR^3)N(R^2)(R^{4b})CO$_2$R^{5b}
S35.3

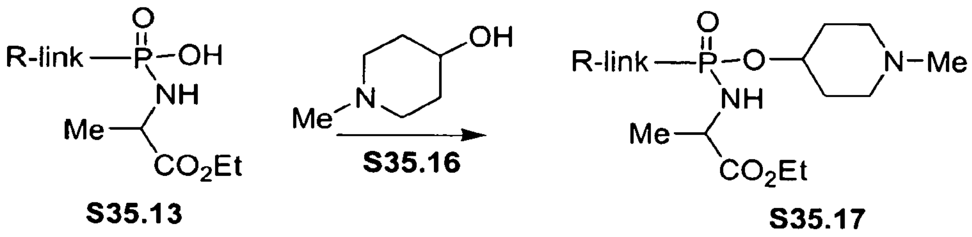
Scheme 35 Example 1


R-link—P(O)(OPh)OH
S35.7
R-link—P(O)(OPh)Cl
S35.8
H$_2$NCH(Me)CO$_2$Et
S35.9
R-link—P(O)(OPh)NH—CH(Me)CO$_2$Et
S35.10

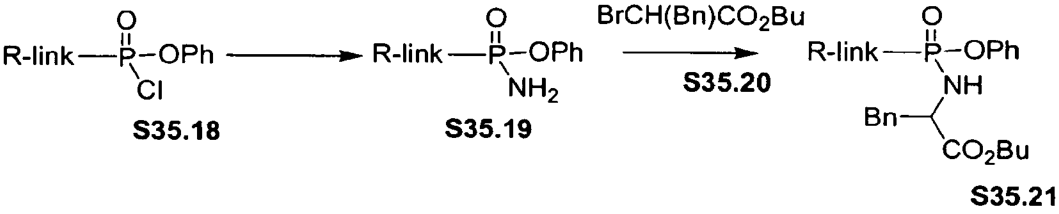
Scheme 35 Example 2


R-link—P(O)(OBn)OH
S35.11
R-link—P(O)(OBn)NH—CH(Me)CO$_2$Et
S35.12
R-link—P(O)(OH)NH—CH(Me)CO$_2$Et
S35.13
CF$_3$CH$_2$OH
S35.14
R-link—P(O)(OCH$_2$CF$_3$)NH—CH(Me)CO$_2$Et
S35.15

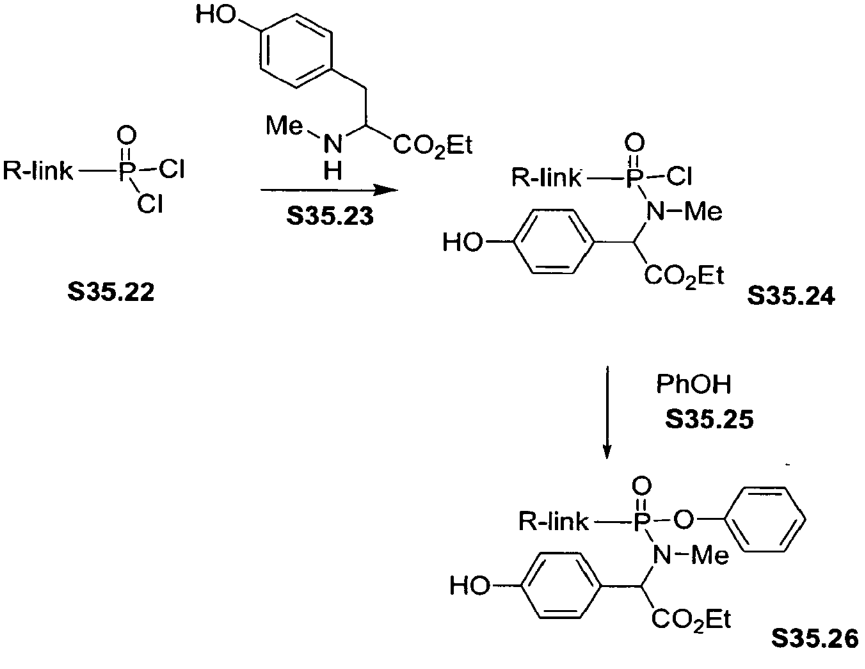
Scheme 35 Example 3


R-link—P(O)(OH)—NH—CH(Me)CO2Et
S35.13
S35.16
R-link—P(O)(NH—CH(Me)CO2Et)—O—N-Me
S35.17

Scheme 35 Example 4


R-link—P(O)(OPh)Cl
S35.18
R-link—P(O)(OPh)NH2
S35.19
BrCH(Bn)CO2Bu
S35.20
R-link—P(O)(OPh)—NH—CH(Bn)CO2Bu
S35.21

Scheme 35 Example 5


HO
Me
N
H
CO2Et
S35.23
R-link—P(O)Cl2
S35.22
R-link—P(O)(Cl)—N-Me
HO
CO2Et
S35.24
PhOH
S35.25
R-link—P(O)(O-Ph)—N-Me
HO
CO2Et
S35.26

Scheme 36 illustrates methods for the preparation of carboalkoxy-substituted phosphonate diesters in which one of the ester groups incorporates a carboalkoxy substituent.

In one procedure, a phosphonate monoester **S34.1**, prepared as described above, is coupled, using one of the methods described above, with a hydroxyester **S36.1**, in which the groups R^{4b} and R^{5b} are as described in Scheme 34. For example, equimolar amounts of the reactants are coupled in the presence of a carbodiimide such as dicyclohexyl carbodiimide, as described in *Aust. J. Chem.*, 1963, 609, optionally in the presence of dimethylaminopyridine, as described in *Tet.*, 1999, 55, 12997. The reaction is conducted in an inert solvent at ambient temperature.

The procedure is illustrated in Scheme 36, Example 1. In this method, a monophenyl phosphonate **S36.9** is coupled, in dichloromethane solution in the presence of dicyclohexyl carbodiimide, with ethyl 3-hydroxy-2-methylpropionate **S36.10** to yield the phosphonate mixed diester **S36.11**.

Using this procedure, but employing, in place of ethyl 3-hydroxy-2-methylpropionate **S36.10**, different hydroxyesters **S33.1**, the corresponding products **S33.2** are obtained.

The conversion of a phosphonate monoester **S34.1** into a mixed diester **S36.2** is also accomplished by means of a Mitsunobu coupling reaction with the hydroxyester **S36.1**, as described in *Org. Lett.*, 2001, 643. In this method, the reactants **S34.1** and **S36.1** are combined in a polar solvent such as tetrahydrofuran, in the presence of a triarylphosphine and a dialkyl azodicarboxylate, to give the mixed diester **S36.2**. The R^1 substituent is varied by cleavage, using the methods described previously, to afford the monoacid product **S36.3**. The product is then coupled, for example using methods described above, with the hydroxy compound R^3OH, to give the diester product **S36.4**.

The procedure is illustrated in Scheme 36, Example 2. In this method, a monoallyl phosphonate **S36.12** is coupled in tetrahydrofuran solution, in the presence of triphenylphosphine and diethylazodicarboxylate, with ethyl lactate **S36.13** to give the mixed diester **S36.14**. The product is reacted with tris(triphenylphosphine) rhodium chloride (Wilkinson catalyst) in acetonitrile, as described previously, to remove the allyl group and produce the monoacid product **S36.15**. The latter compound is then coupled, in pyridine solution at ambient temperature, in the presence of dicyclohexyl carbodiimide, with one molar equivalent of 3-hydroxypyridine **S36.16** to yield the mixed diester **S36.17**.

Using the above procedures, but employing, in place of the ethyl lactate **S36.13** or 3-hydroxypyridine, a different hydroxyester **S36.1** and/or a different hydroxy compound R^3OH, the corresponding products **S36.4** are obtained.

The mixed diesters **S36.2** are also obtained from the monoesters **S34.1** via the intermediacy of the activated monoesters **S36.5**. In this procedure, the monoester **S34.1** is converted into the activated compound **S36.5** by reaction with, for example, phosphorus pentachloride, as described in *J. Org. Chem.*, 2001, 66, 329, or with thionyl chloride or oxalyl chloride (Lv = Cl), or with triisopropylbenzenesulfonyl chloride in pyridine, as described in *Nucleosides and Nucleotides*, 2000, 19, 1885, or with carbonyl diimidazole, as described in *J. Med. Chem.*, 2002, 45, 1284. The resultant activated monoester is then reacted with the hydroxyester **S36.1**, as described above, to yield the mixed diester **S36.2**.

The procedure is illustrated in Scheme 36, Example 3. In this sequence, a monophenyl phosphonate **S36.9** is reacted, in acetonitrile solution at 70 °C, with ten equivalents of thionyl chloride, so as to produce the phosphoryl chloride **S36.19**. The product is then reacted with ethyl 4-carbamoyl-2-hydroxybutyrate **S36.20** in dichloromethane containing triethylamine, to give the mixed diester **S36.21**.

Using the above procedures, but employing, in place of ethyl 4-carbamoyl-2-hydroxybutyrate **S36.20**, different hydroxyesters **S36.1**, the corresponding products **S36.2** are obtained.

The mixed phosphonate diesters are also obtained by an alternative route for incorporation of the R^3O group into intermediates **S36.3** in which the hydroxyester moiety is already incorporated. In this procedure, the monoacid intermediate **S36.3** is converted into the activated derivative **S36.6** in which Lv is a leaving group such as chloro, imidazole, and the like, as previously described. The activated intermediate is then reacted with the hydroxy compound R^3OH, in the presence of a base, to yield the mixed diester product **S36.4**.

The method is illustrated in Scheme 36, Example 4. In this sequence, the phosphonate monoacid **S36.22** is reacted with trichloromethanesulfonyl chloride in tetrahydrofuran containing collidine, as described in *J. Med. Chem.*, 1995, 38, 4648, to produce the trichloromethanesulfonyloxy product **S36.23**. This compound is reacted with 3-(morpholinomethyl)phenol **S36.24** in dichloromethane containing triethylamine, to yield the mixed diester product **S36.25**.

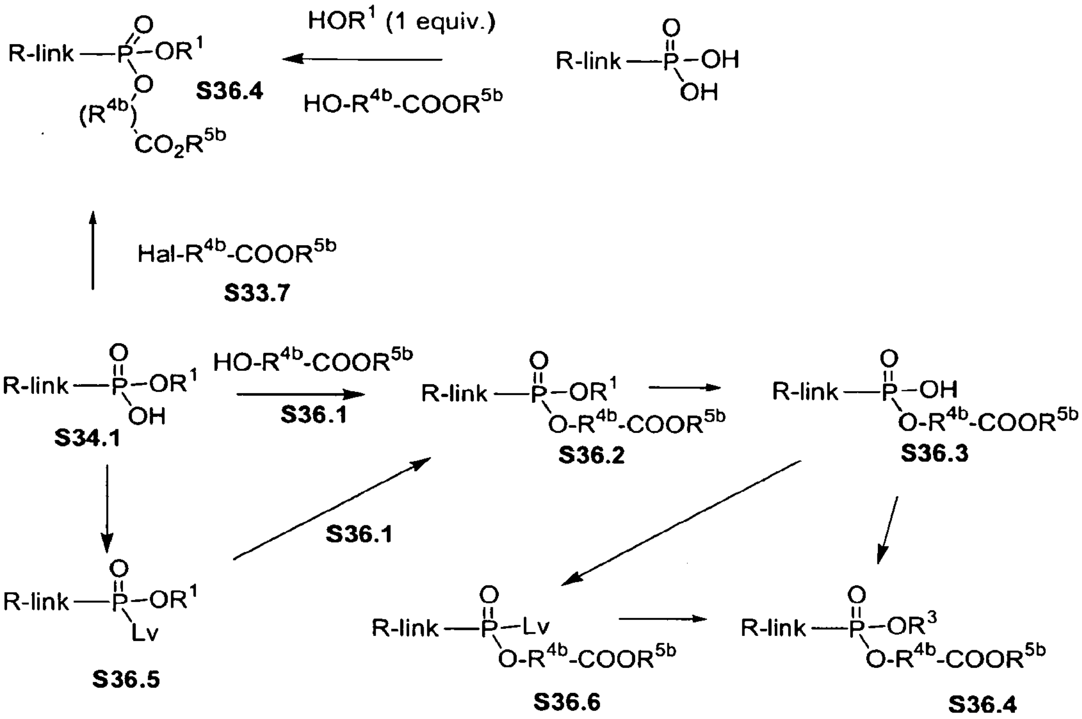
Using the above procedures, but employing, in place of with 3-(morpholinomethyl)phenol **S36.24**, different alcohols R^3OH, the corresponding products **S36.4** are obtained.

The phosphonate esters **S36.4** are also obtained by means of alkylation reactions performed on the monoesters **S34.1**. The reaction between the monoacid **S34.1** and the haloester **S36.7** is performed in a polar solvent in the presence of a base such as diisopropylethylamine, as described in *Anal. Chem.*, 1987, 59, 1056, or triethylamine, as described in *J. Med. Chem.*, 1995, 38, 1372, or in a non-polar solvent such as benzene, in the presence of 18-crown-6, as described in *Syn. Comm.*, 1995, 25, 3565.

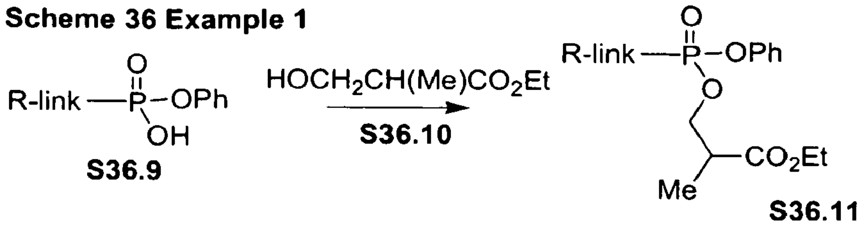
The method is illustrated in Scheme 36, Example 5. In this procedure, the monoacid **S36.26** is reacted with ethyl 2-bromo-3-phenylpropionate **S36.27** and diisopropylethylamine in dimethylformamide at 80 °C to afford the mixed diester product **S36.28**.

Using the above procedure, but employing, in place of ethyl 2-bromo-3-phenylpropionate **S36.27**, different haloesters **S36.7**, the corresponding products **S36.4** are obtained.

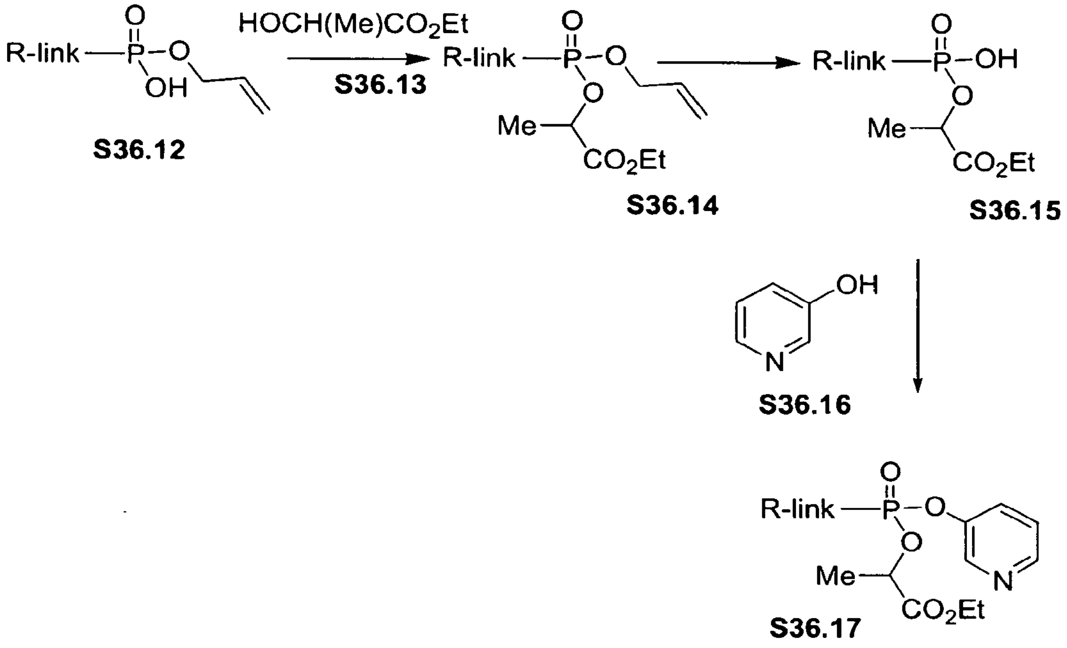
Scheme 36


R-link
HOR^1 (1 equiv.)
HO-R^{4b}-COOR^{5b}
S36.4
Hal-R^{4b}-COOR^{5b}
S33.7
S34.1
S36.1
S36.2
S36.3
S36.5
S36.6
S36.4

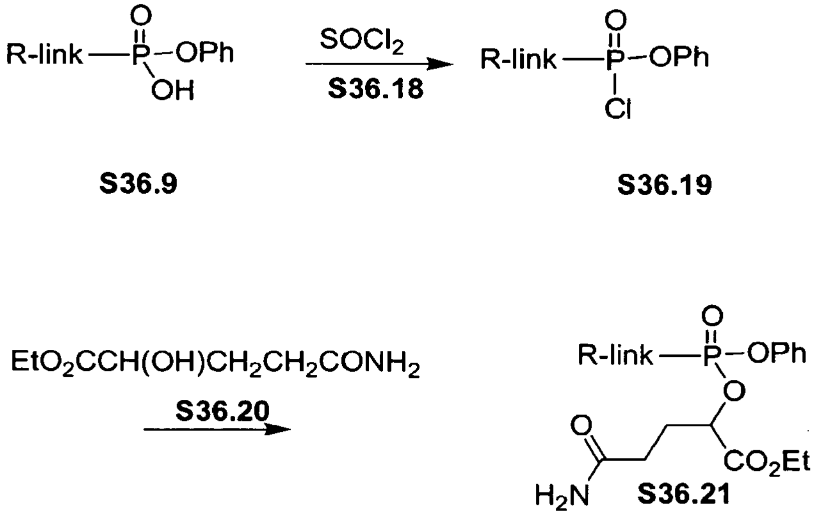
Scheme 36 Example 1


R-link
OPh
OH
S36.9
HOCH2CH(Me)CO2Et
S36.10
R-link
OPh
CO2Et
Me
S36.11

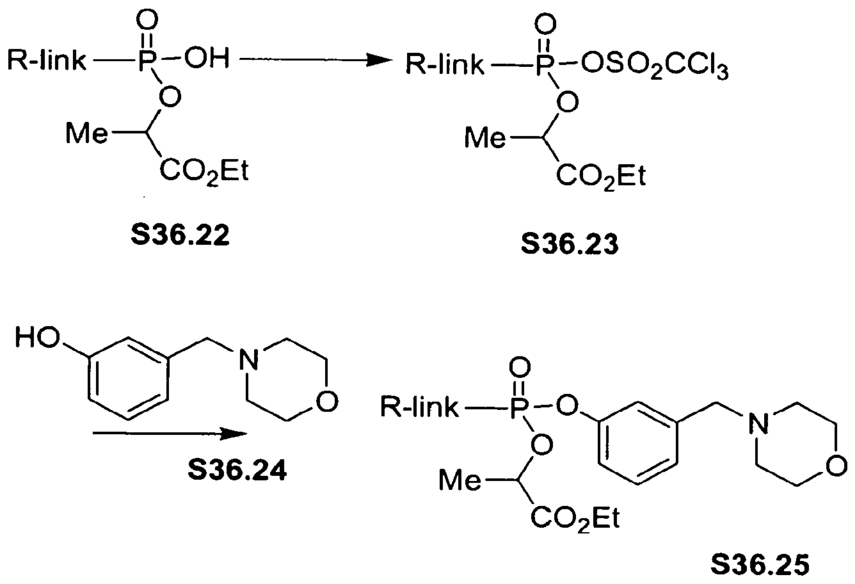
Scheme 36 Example 2


R-link
OH
S36.12
HOCH(Me)CO2Et
S36.13
R-link
Me
CO2Et
S36.14
R-link
OH
Me
CO2Et
S36.15
OH
N
S36.16
R-link
Me
N
CO2Et
S36.17

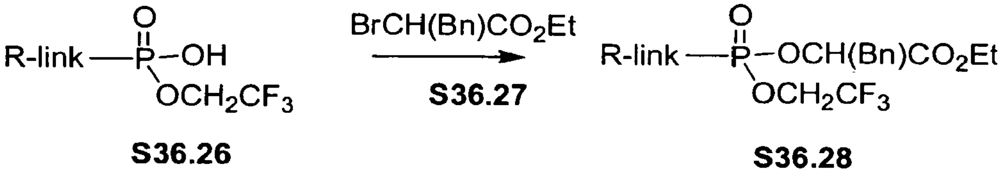
Scheme 36 Example 3


R-link
OPh
OH
SOCl2
S36.18
R-link
OPh
Cl
S36.9
S36.19
EtO2CCH(OH)CH2CH2CONH2
S36.20
R-link
OPh
H2N
CO2Et
S36.21

Scheme 36 Example 4



Scheme 36 Example 5



Scheme 37 illustrates methods for the preparation of phosphonate diesters in which both the ester substituents incorporate carboalkoxy groups.

The compounds are prepared directly or indirectly from the phosphonic acids **S34.6**. In one alternative, the phosphonic acid is coupled with the hydroxyester **S37.2**, using the conditions described previously in Schemes 34-36, such as coupling reactions using dicyclohexyl carbodiimide or similar reagents, or under the conditions of the Mitsunobu reaction, to afford the diester product **S37.3** in which the ester substituents are identical.

This method is illustrated in Scheme 37, Example 1. In this procedure, the phosphonic acid **S34.6** is reacted with three molar equivalents of butyl lactate

S37.5 in the presence of Aldrithiol-2 and triphenyl phosphine in pyridine at ca. 70 °C, to afford the diester **S37.6**.

Using the above procedure, but employing, in place of butyl lactate **S37.5**, different hydroxyesters **S37.2**, the corresponding products **S37.3** are obtained.

Alternatively, the diesters **S37.3** are obtained by alkylation of the phosphonic acid **S34.6** with a haloester **S37.1**. The alkylation reaction is performed as described in Scheme 36 for the preparation of the esters **S36.4**.

This method is illustrated in Scheme 37, Example 2. In this procedure, the phosphonic acid **S34.6** is reacted with excess ethyl 3-bromo-2-methylpropionate **S37.7** and diisopropylethylamine in dimethylformamide at ca. 80 °C, as described in *Anal. Chem.*, 1987, 59, 1056, to produce the diester **S37.8**.

Using the above procedure, but employing, in place of ethyl 3-bromo-2-methylpropionate **S37.7**, different haloesters **S37.1**, the corresponding products **S37.3** are obtained.

The diesters **S37.3** are also obtained by displacement reactions of activated derivatives **S34.7** of the phosphonic acid with the hydroxyesters **S37.2**. The displacement reaction is performed in a polar solvent in the presence of a suitable base, as described in Scheme 36. The displacement reaction is performed in the presence of an excess of the hydroxyester, to afford the diester product **S37.3** in which the ester substituents are identical, or sequentially with limited amounts of different hydroxyesters, to prepare diesters **S37.3** in which the ester substituents are different.

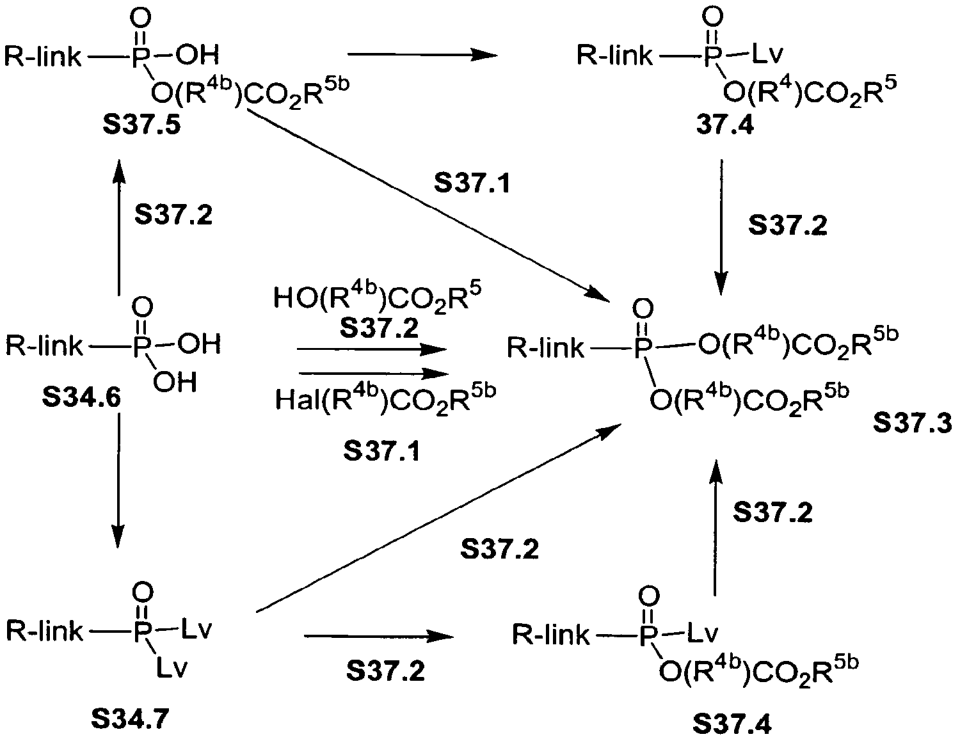
The methods are illustrated in Scheme 37, Examples 3 and 4. As shown in Example 3, the phosphoryl dichloride **S35.22** is reacted with three molar equivalents of ethyl 3-hydroxy-2-(hydroxymethyl)propionate **S37.9** in tetrahydrofuran containing potassium carbonate, to obtain the diester product **S37.10**.

Using the above procedure, but employing, in place of ethyl 3-hydroxy-2-(hydroxymethyl)propionate **S37.9**, different hydroxyesters **S37.2**, the corresponding products **S37.3** are obtained.

Scheme 37, Example 4 depicts the displacement reaction between equimolar amounts of the phosphoryl dichloride **S35.22** and ethyl 2-methyl-3-hydroxypropionate **S37.11**, to yield the monoester product **S37.12**. The reaction is conducted in acetonitrile at 70° in the presence of diisopropylethylamine. The product **S37.12** is then reacted, under the same conditions, with one molar equivalent of ethyl lactate **S37.13**, to give the diester product **S37.14**.

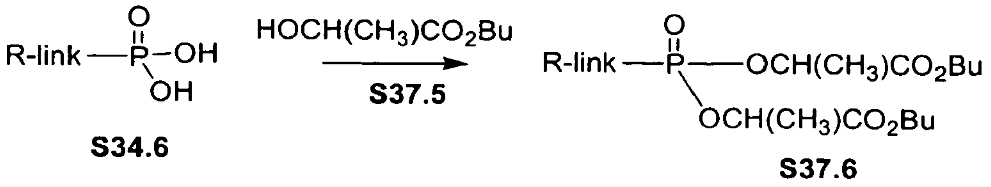
Using the above procedures, but employing, in place of ethyl 2-methyl-3-hydroxypropionate **S37.11** and ethyl lactate **S37.13**, sequential reactions with different hydroxyesters **S37.2**, the corresponding products **S37.3** are obtained.

Scheme 37

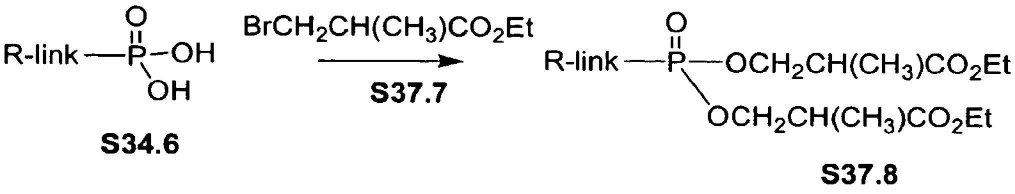


S37.5
37.4
S37.1
S37.2
S37.2
HO(R4b)CO2R5
S37.2
Hal(R4b)CO2R5b
S37.1
S34.6
S37.3
S37.2
S37.2
S37.2
S34.7
S37.4

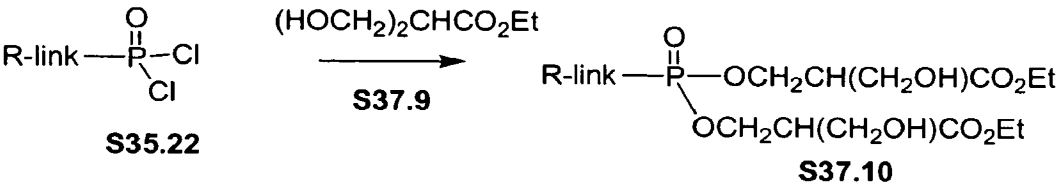
Scheme 37 Example 1


R-link
HOCH(CH3)CO2Bu
S37.5
S34.6
S37.6

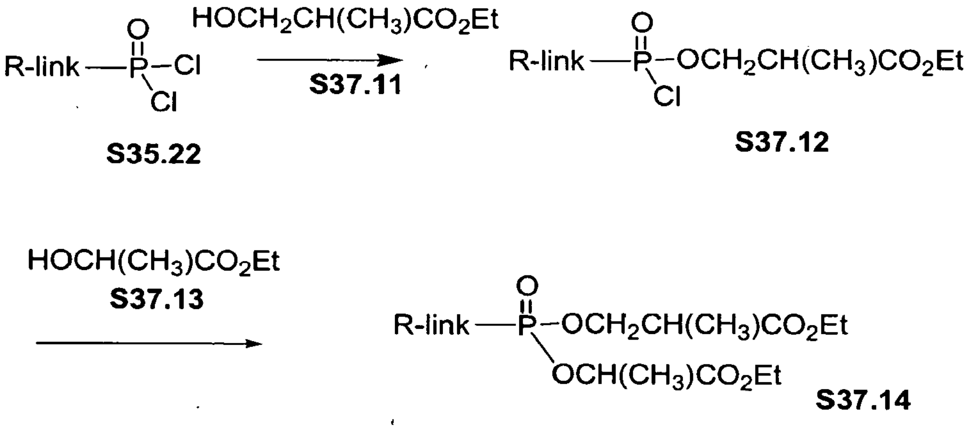
Scheme 37 Example 2


R-link
BrCH2CH(CH3)CO2Et
S37.7
S34.6
S37.8

Scheme 37 Example 3


R-link
(HOCH2)2CHCO2Et
S37.9
S35.22
S37.10

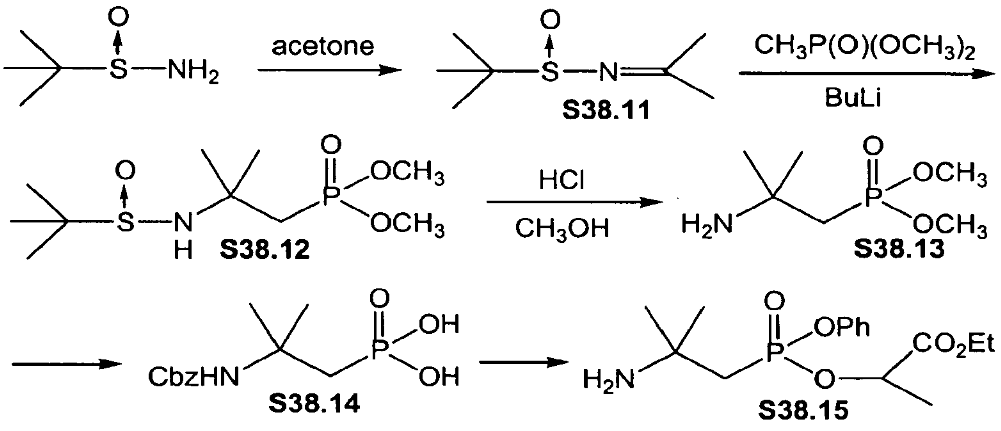
Scheme 37 Example 4


R-link
HOCH2CH(CH3)CO2Et
S37.11
S35.22
S37.12
HOCH(CH3)CO2Et
S37.13
S37.14

2,2-Dimethyl-2-aminoethylphosphonic acid intermediates can be prepared by the route in Scheme 5. Condensation of 2-methyl-2-propanesulfinamide with acetone give sulfinyl imine **S38.11** (*J. Org. Chem.* **1999**, *64*, 12). Addition of dimethyl methylphosphonate lithium to **S38.11** afford **S38.12**. Acidic methanolysis of **S38.12** provide amine **S38.13**. Protection of amine with Cbz group and removal of methyl groups yield phosphonic acid

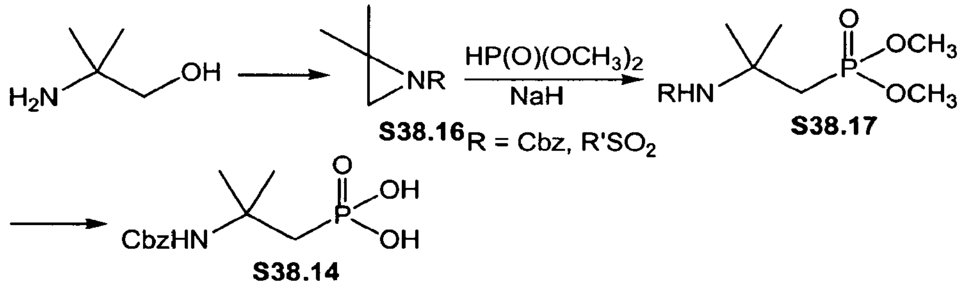
S38.14, which can be converted to desired **S38.15** (Scheme 38a) using methods reported earlier on. An alternative synthesis of compound **S38.14** is also shown in Scheme 38b. Commercially available 2-amino-2-methyl-1-propanol is converted to aziridines **S38.16** according to literature methods (*J. Org. Chem.* **1992**, *57*, 5813; *Syn. Lett.* **1997**, *8*, 893). Aziridine opening with phosphite give **S38.17** (*Tetrahedron Lett.* **1980**, *21*, 1623). Reprotection) of **S38.17** affords **S38.14**.

Scheme 38a



O
S—NH2
acetone
S—N
S38.11
CH3P(O)(OCH3)2
BuLi
S—N
H
S38.12
OCH3
OCH3
HCl
CH3OH
H2N
S38.13
CbzHN
OH
OH
S38.14
H2N
OPh
CO2Et
S38.15

Scheme 38b



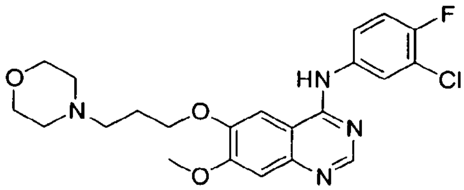
H2N
OH
NR
S38.16 R = Cbz, R'SO2
HP(O)(OCH3)2
NaH
RHN
OCH3
OCH3
S38.17
CbzHN
OH
OH
S38.14

The invention will now be illustrated by the following non-limiting Examples.

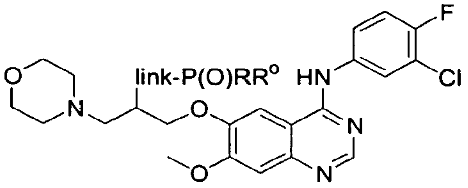
Example 1

Synthesis of Representative Compounds of Formulae 1-3

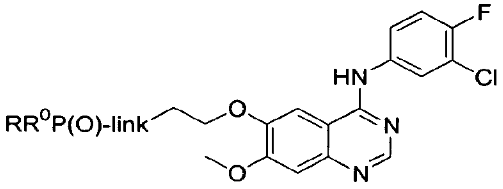
Generally, compounds of the invention can be made as illustrated below:


F
HN
Cl
O
N
O
N
O
N

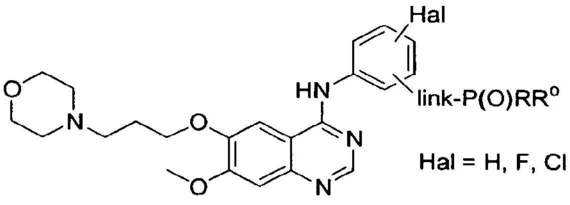
Gefitinib / Iressa / ZD-1839
US-5770596


F
O
N
link-P(O)RR^0
HN
Cl
O
N
O
N

1.1

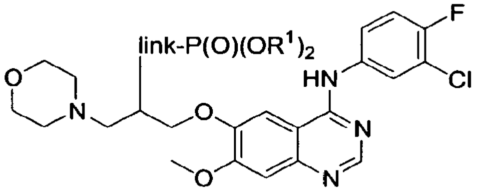

F
HN
Cl
RR^{0}P(O)-link
O
N
O
N

1.2

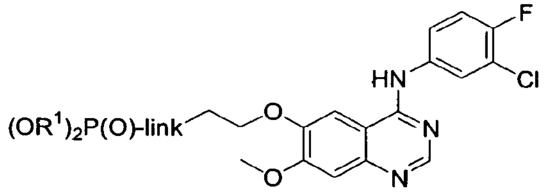

Hal
O
HN
link-P(O)RR^0
N
O
N
O
N

Hal = H, F, Cl

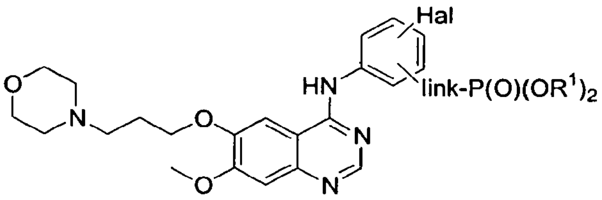
1.3


F
link-P(O)(OR^1)$_2$
O
HN
Cl
N
O
N
O
N

1.4

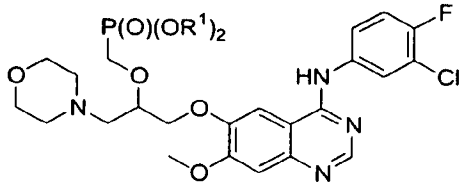

F
HN
Cl
(OR^1)$_2$P(O)-link
O
N
O
N

1.5

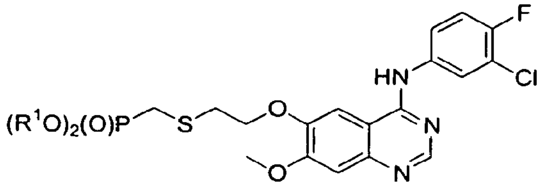

Hal
O
HN
link-P(O)(OR^1)$_2$
N
O
N
O
N

1.6 Hal = H, F, Cl

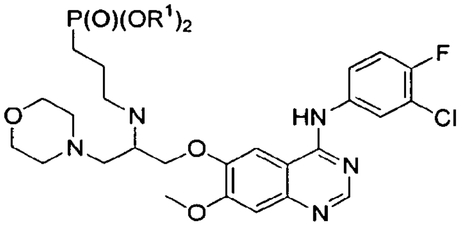
R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl



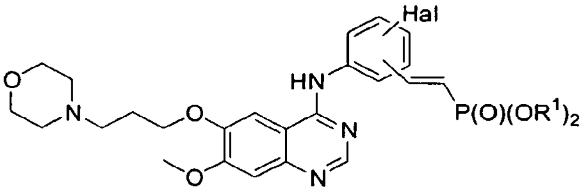
1.7



1.8



1.9



Hal = H, F, Cl

1.10

Phosphonate Interconversions

Phosphonate interconversions of representative compounds of the invention can be prepared as discussed hereinbelow. The final compounds, described above as **1.1**, **1.2** and **1.3**, are synthesized according to the methods described herein. The intermediate phosphonate esters, shown as **1.4**, **1.5** and **1.6**, can be used to prepare the final compounds by one skilled in the art using known methods for synthesis of substituted phosphonates. These methods are similar to those described for the synthesis of amides. The preparation of amides from carboxylic acids and derivatives is described, for example, in "Organic Functional Group Preparations," by S.R. Sandler and W. Karo, Academic Press, 1968, p. 274. Further methods are described below for the synthesis of the phosphonate diesters and can, in some cases, be applied to the synthesis of phosphor-amides.

The conversion of various substituents into the group link-$P(O)(OR^1)_2$, where R^1 is defined above as **1.4**, **1.5** and **1.6**, or indeed the final stage of $P(O)RR^o$, as defined above, can be effected at any convenient stage of the synthetic sequence, or in the final step. The selection of an appropriate step for the introduction of the phosphonate substituent is made after consideration of the chemical procedures required, and the stability of the substrates to those procedures. It may be necessary to protect reactive groups, for example hydroxyl, amino, during the introduction of the group link-$P(O)(OR^1)_2$ or $P(O)RR^o$.

In the succeeding examples, the nature of the phosphonate ester group $P(O)(OR^1)_2$ can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below.

Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1996. Reactive substituents that may be protected are shown in the accompanying schemes as, for example, [OH], [SH], *etc.*

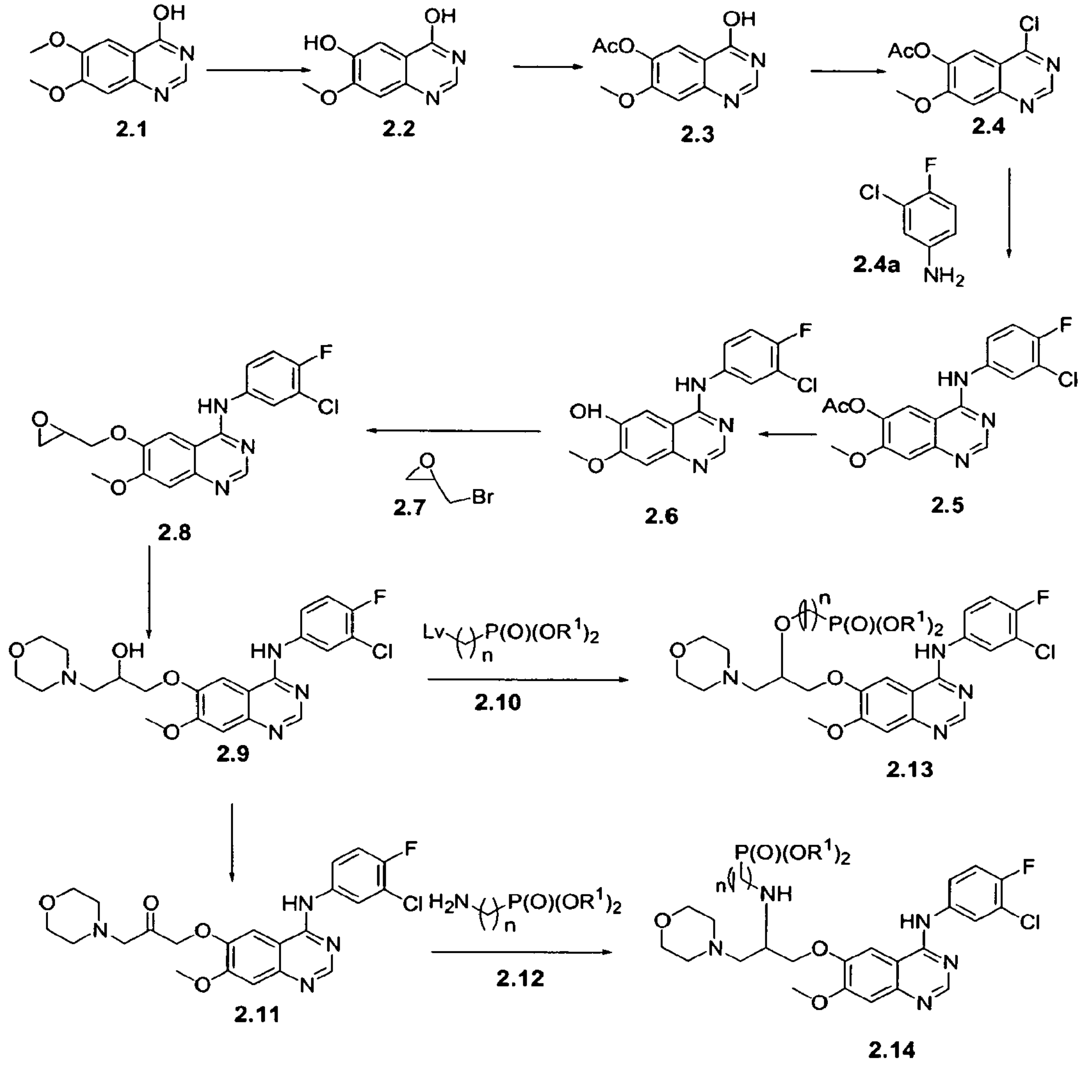
General applicability of methods for introduction of phosphonate substituents.

The procedures described herein for the introduction of phosphonate moieties are, with appropriate modifications known to one skilled in the art, transferable to different chemical substrates. Thus, the methods described herein below for the introduction of phosphonate groups onto compounds of the invention are also applicable to the introduction of phosphonate moieties onto anilines of the invention and the reverse is also true.

Example 2

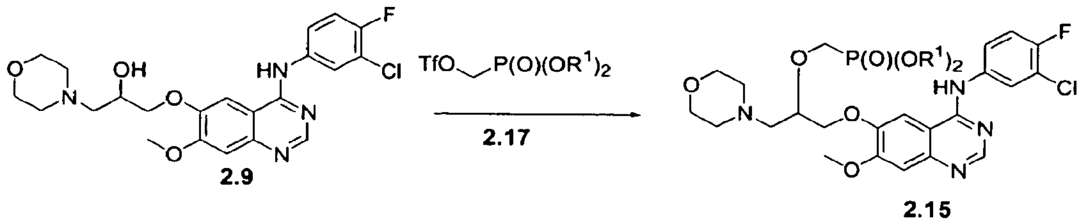
Synthesis of Representative Compounds of Formulae 1-3

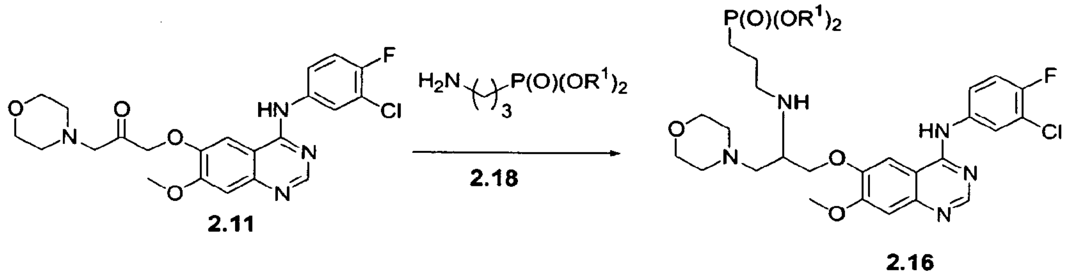
Intermediate phosphonates of representative compounds of the invention can be made as described herein. For example, the synthesis of target molecules such as **1.4** (Example 1), in which the link is a heteroatom and carbon chain can be illustrated as follows:



The preparation of **2.1** is described in U.S. Patent No. 5,770,596. Diether **2.1** is converted into mono ether **2.2** as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M Wuts, Wiley, 3rd Edition, 1999, p. 246, or by the method described in U.S. Patent No. 5,770,596. In one embodiment, diether **2.1** in methanesulfonic acid is treated with L-methionine at reflux to give the phenol **2.2**. Phenol **2.2** is then protected as the acetyl compound **2.3** and then converted to the chloride **2.4**. These procedures are described in U.S. Patent No. 5,770,596. The acetoxy compound is then treated with the aniline **2.4a** to give the amine **2.5** followed by deprotection of the acetyl group to give **2.6** as described in U.S. Patent No. 5,770,596. Treatment of **2.6** with epibromohydrin **2.7** (Aldrich) in DMF with potassium carbonate present then affords the epoxide **2.8.** Treatment of epoxide **2.8** with morpholine in a non-protic solvent as reflux in the presence of a base such as triethylamine affords the alcohol **2.9.** The alcohol **2.9** is treated with one equivalent of the phosphonate alkylating agent, in which Lv is a group such as mesyl, trifluoromethanesulfonyl, Br, I, Cl, tosyl, *etc.*, in the presence of base *e.g.*, potassium or cesium carbonate in DMF, to give the ether **2.13** in which the link is an oxygen and carbon chain. Alternatively, the alcohol **2.9** is oxidized to the ketone **2.11**, as described in "Comprehensive Organic Transformations," by R. C. Larock, 2nd Edition, 1999, p.1234ff. Preferably, the alcohol **2.9** is treated with Dess-martin periodinone to give the ketone **2.11**. Ketone **2.11** is then reacted with an amino alkyl phosphonate **2.12** under reductive amination conditions to give the phosphonate **2.14** in which the link is a nitrogen and carbon chain. The preparation of amines by means of reductive amination procedures is described, for example, in "Comprehensive Organic Transformations," by R. C. Larock, 2nd edition, p. 835. In this procedure, the amine component and the aldehyde component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product.

Specific compounds of the invention can be prepared as follows.



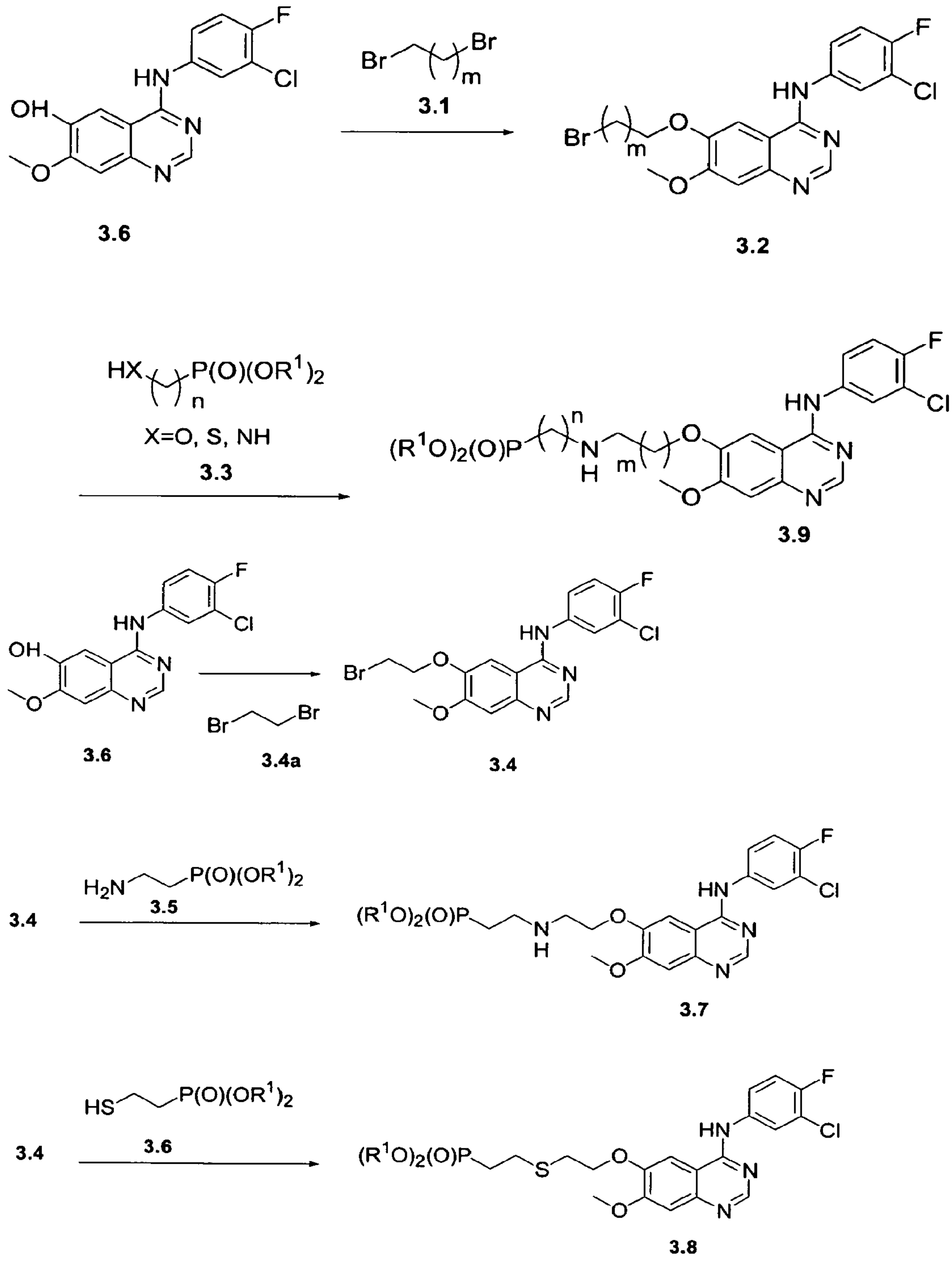


The alcohol **2.9** is treated with triflate **2.17**, prepared as described in *Tet. Lett.*, 27:1497 (1986), and potassium carbonate in DMF, to give the ether **2.15.** Alternatively, for example, the ketone **2.11** is treated with amine **2.18** (Acros) in methanol. After a period of time, sodium borohydride is added to give the amine **2.16**. Using the above procedures, but employing in place of the triflate **2.17** or the amine **2.18**, additional compounds of the invention are obtained.

Example 3

Synthesis of Representative Compounds of Formulae 1-3

Representative compounds of the invention can be prepared as follows:


3.6
Br
Br
m
3.1
3.2
HX
P(O)(OR1)2
n
X=O, S, NH
3.3
(R1O)2(O)P
N
H
m
3.9
3.6
3.4a
3.4
3.4
H2N
P(O)(OR1)2
3.5
3.7
3.4
HS
P(O)(OR1)2
3.6
S
3.8

The reactions shown above illustrate the preparation of the compounds **3.9** of the invention in which the phosphonate is linked through a carbon chain and a heteroatom.

Phenol **3.6** (See also phenol **2.6** in Example **2**) is treated with dibromide **3.1** using the conditions described in Example **2** for the preparation of **2.8** from **2.6**, to give bromide **3.2**. Bromide **3.2** is then treated with the dialkyl hydroxy, thio or amino-substituted alkylphosphonate **3.3** to give the product **3.9**. The reaction is performed in the presence of a base, in a polar aprotic solvent such as dioxan or N-methylpyrrolidinone. The base employed in the reaction depends on the nature of the reactant **3.3**. For example, if X is O, a strong base such as, for example, lithium hexamethyldisilylazide or potassium tert. butoxide is employed. If X is S, NH or N-alkyl, an inorganic base such as cesium carbonate and the like is employed.

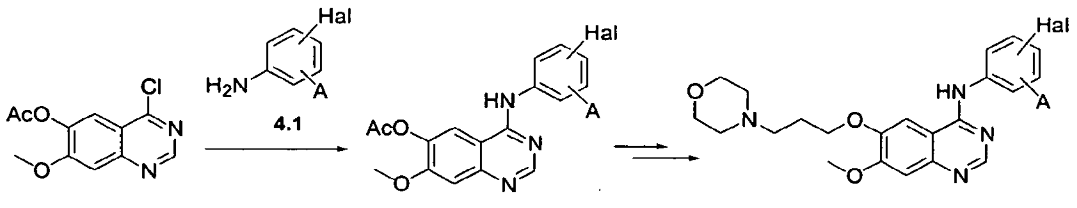
A specific compound of the invention can be prepared as follows. **3.6** is treated with dibromoethane **3.4a** to give the bromide **3.4**. Bromide **3.4** is then treated with amine **3.5**, prepared as described in J. Org. Chem., 65:676 (2000), in DMF and potassium carbonate at about 80°C to give the phosphonate **3.7**.

Alternatively, bromide **3.4** is then heated at reflux with an equimolar amount of a dialkyl 2-mercaptoethylphophonate **3.7**, the preparation of which is described in Aust. J. Chem., 43:1123 (1990), in the presence of sodium carbonate, to afford the thioether product **3.8**.

Using the above procedures, but employing, in place of the dibromoethane **3.4a**, different dibromo compounds **3.1** and/or different alkyl phosphonates **3.3** in place of **3.5** or **3.7** the corresponding products **3.8** are obtained.

Example 4

Synthesis of Representative Compounds of Formulae 1-3

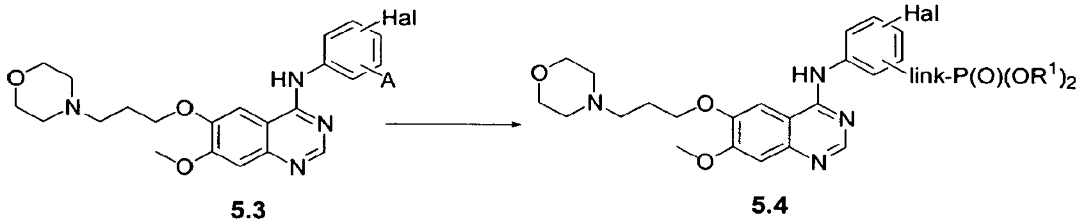


4.4 4.2 4.3

The synthesis of target molecules **1.6** (see Example **1**), in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR^1)$_2$ is illustrated above. The preparation of **4.4** is described in Example **2**. Treatment of chloride **4.4** with amine **4.1** in reluxing isopropanol gives amine **4.2**. The preparation of **4.1** in which A is group link-P(O)(OR^1)$_2$ is described below. Treatment of amine **4.2** according to conditions described in U.S. Patent No. 5,770.599 then affords the final product **4.3**.

Example 5

Synthesis of Representative Compounds of Formulae 1-3



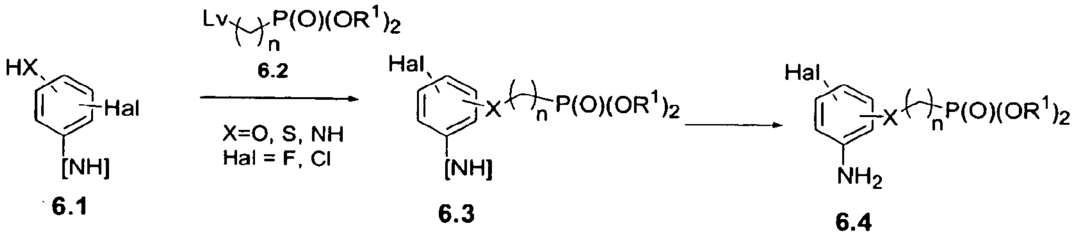
5.3 **5.4**

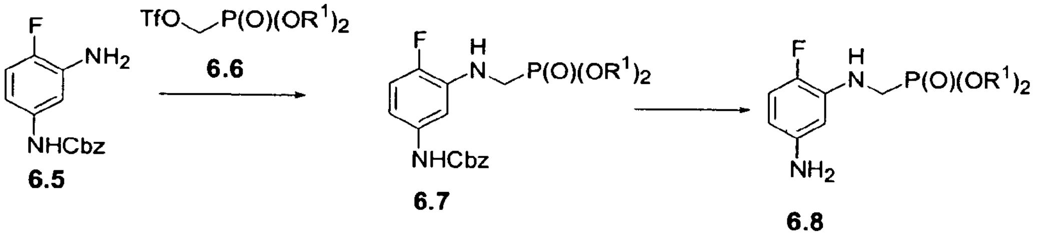
The preparation of the compounds **5.3** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br, *etc.*, is shown. The conversion of the compounds **5.3** in which A is [OH], [SH], [NH], Br, *etc.*, into the phosphonate esters **5.4** is illustrated. In this procedure, the compounds **5.3** are converted, using the procedures described herein into the compounds **5.4**.

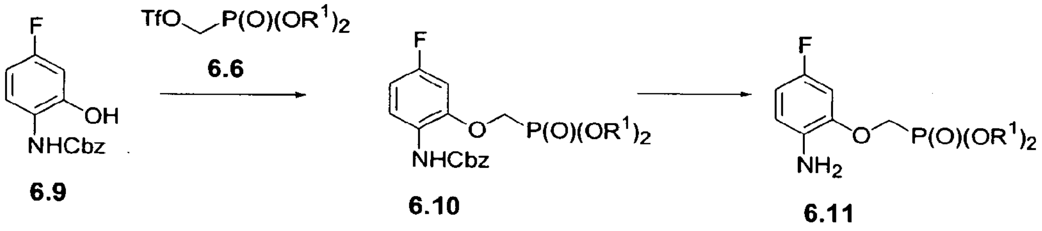
Example 6

Synthesis of Representative Compounds of Formulae 1-3

The preparation of phosphonate-containing derivatives which are employed in the preparation of the phosphonate ester intermediates of the invention is described herein.


HX
Hal
[NH]
6.1
Lv P(O)(OR¹)₂
n
6.2
X=O, S, NH
Hal = F, Cl
Hal
X
n
P(O)(OR¹)₂
[NH]
6.3
Hal
X
n
P(O)(OR¹)₂
NH₂
6.4


F
NH₂
NHCbz
6.5
TfO P(O)(OR¹)₂
6.6
F
H
N P(O)(OR¹)₂
NHCbz
6.7
F
H
N P(O)(OR¹)₂
NH₂
6.8


F
OH
NHCbz
6.9
TfO P(O)(OR¹)₂
6.6
F
O P(O)(OR¹)₂
NHCbz
6.10
F
O P(O)(OR¹)₂
NH₂
6.11

The preparation of representative compounds of the invention in which the phosphonate is attached through a heteroatom, *e.g.*, O, S, or N, and a carbon linker is illustrated. In this procedure an optionally protected aniline is reacted with an alkylphosphonate **6.2** in which Lv is a leaving group such as triflate, Br, Cl, Mesyl, *etc.*, in the presence of a suitable base. The base required for this transformation depends on the nature of the heteroatom X. For example, if X is N or S, an excess of an inorganic base such as, for example, potassium carbonate, in the presence of an organic solvent such as dimethylformamide, is suitable. The reaction proceeds at from ambient temperature to about 80° to afford the displacement products **6.3**. If X is O, an equimolar amount of a strong base, such as, for example, lithium hexamethyldisilylazide and the like, is employed in the presence of a solvent such as tetrahydrofuran. Deprotection of the amine group, as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 ch 7. affords the amine **6.4**.

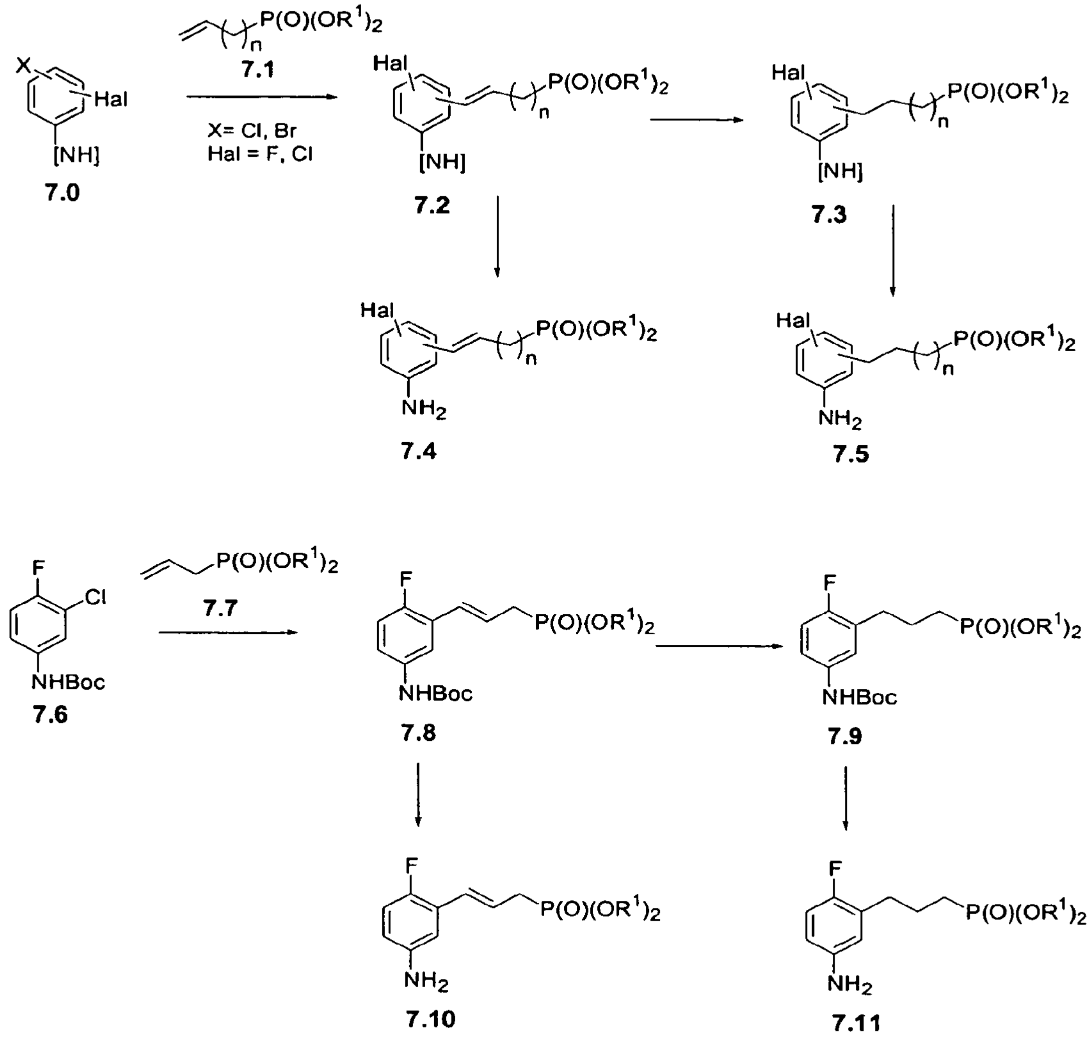
A specific compound of the invention can be prepared as follows. The diamine **6.5** (Aldrich), protected as the CBZ carbamate (see "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, p531ff) is treated with an equimolar amount of triflate **6.6**, the preparation of which is described in _Tet. Lett._, 27:1497 (1986) in dimethylformamide containing excess potassium carbonate, at about 60°C to afford the phosphonate product **6.7**. Deprotection by reduction over palladium on carbon in the presence of hydrogen then affords the amine **6.8.**

Alternatively, the aminophenol **6.9**, protected as the CBZ carbamate as described above, is reacted with one equivalent of triflate **6.6** to give phosphonate **6.10.** Removal of the CBZ group by catalytic reduction over palladium on carbon in the presence of hydrogen, as described above, then affords the amine **6.11.**

Using the above procedures, but employing, in place of the aniline **6.5** or phenol **6.9,** different anilines **6.1**, and/or different alkylphosphonates **6.2**, in place of **6.6**, the corresponding products **6.4** are obtained.

Example 7

Synthesis of Representative Compounds of Formulae 1-3



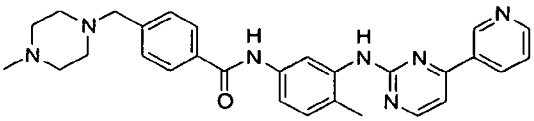
The preparation of compounds of the invention in which the phosphonate is attached through a unsaturated or saturated carbon linker is illustrated. In this procedure, an optionally protected halo-substituted aniline **7.0** is coupled, by means of a palladium-catalyzed Heck reaction with a dialkyl alkenyl phosphonate **7.1**, to afford the coupled product **7.2**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in "Advanced Organic Chemistry," by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12:146 (1979). The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxane, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product **7.2**. Protection of anilines is described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999, ch 7. Preferably, the aniline is treated with a BOC reagent such as BOC chloride or BOC anhydride in the presence of DMAP and a base, *e.g.*, triethylamine, to afford the protected aniline. Optionally, the product **7.2** can be reduced to afford the saturated phosphonate **7.3**. Methods for the reduction of carbon-carbon double bonds are described, for example, in "Comprehensive Organic Transformations," by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, and chemical reduction, the latter for example employing diborane or diimide.

For example, BOC protected 3-chloro-4-fluoro aniline **7.6** (Aldrich) is reacted with a dialkyl propenyl phosphonate **7.7**, the preparation of which is described in *J. Med. Chem.*, 39:949 (1996); in the presence of bis(triphenylphosphine) palladium(II) chloride , as described in *J. Med. Chem.*, 35:1371 (1992), to afford the coupled product **7.8.** The BOC protection of the aniline is performed by treating the corresponding aniline with BOC anhydride in the presence of DMAP. The product **7.8** is reduced, for example by reaction with diimide, as described in *J. Org. Chem.*, 30:3965 (1965), to afford the saturated product **7.9.** Boc removal by treatment of **7.8** and **7.9** with TFA in THF or dioxane affords the products **7.10** and **7.11**, respectively. Using the above procedures but employing in place of the halo pyridine compound **7.6**, different pyridines **7.0** and/or different phosphonates **7.1**, the corresponding products **7.4** and **7.5** are obtained.

Example 8

Synthesis of Representative Compounds of Formulae 4-7

In general, the compounds of the invention described herein can be synthesized as follows:



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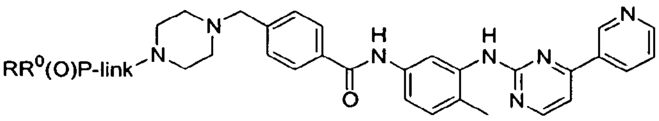
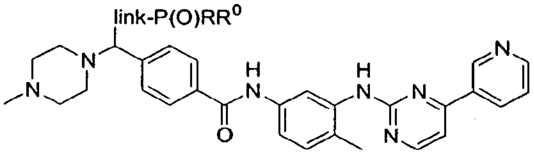
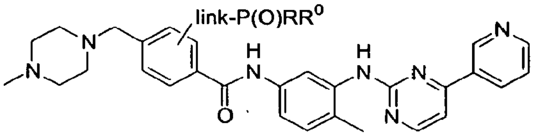


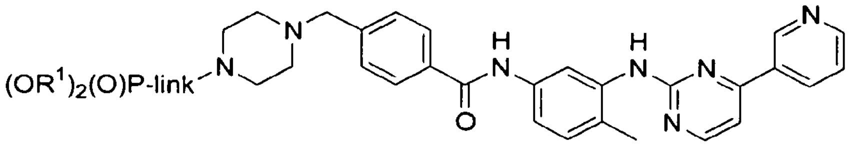
8.1



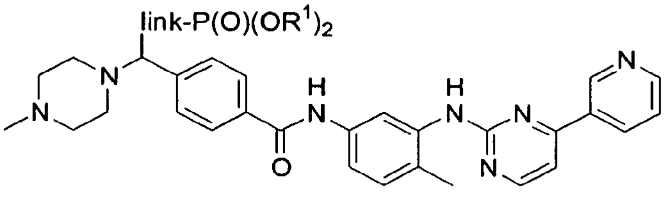
8.2



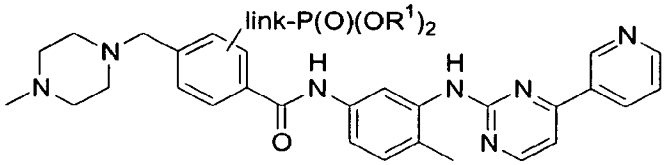
8.3



8.4

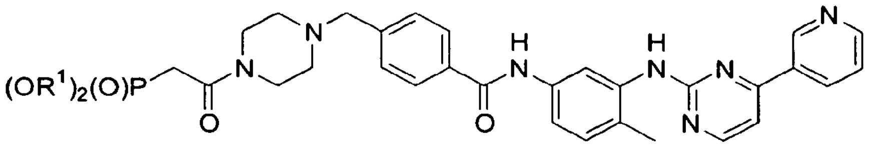


8.5

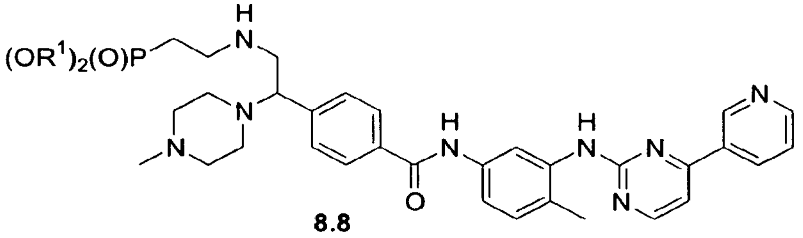


8.6

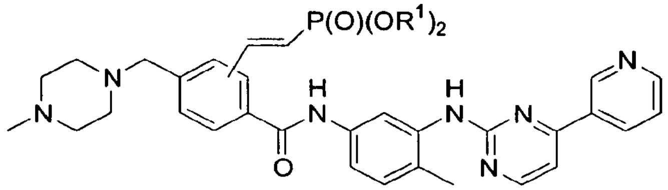
R^1 = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl



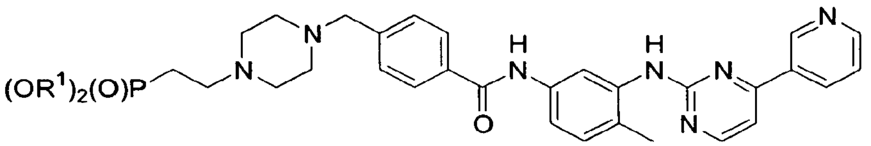
8.7



8.8



8.9



8.10

Phosphonate Interconversions

In general, phosphonate conversions of the representative compounds of the invention, *e.g.*, as illustrated above, can be as follows: The intermediate phosphonate esters shown above (**8.4, 8.5, 8.6**) can be used to prepare the final compounds illustrated above (**8.1, 8.2, 8.3**), by one skilled in the art, using known methods for synthesis of substituted phosphonates. These methods are similar to those described for the synthesis of amides. The preparation of amides from carboxylic acids and derivatives is described, for example, in "Organic Functional Group Preparations," by S.R. Sandler and W. Karo, Academic Press, 1968, p. 274. Further methods are described below for the synthesis of the phosphonate diesters and can in some cases be applied to the synthesis of phosphor-amides.

The conversion of various substituents into the group link-P(O)(OR^1)$_2$, where R^1 is defined above, *e.g.*, see **8.4**, **8.5**, **8.6**, or indeed the final stage of P(O)RR^o, as defined above, can be effected at any convenient stage of the synthetic sequence, or in the final step. The selection of an appropriate step for the introduction of the phosphonate substituent is made after consideration of the chemical procedures required, and the stability of the substrates to those procedures. It may be necessary to protect reactive groups, for example hydroxyl, amino, during the introduction of the group link-P(O)(OR^1)$_2$ or P(O)RR^o.

In the succeeding examples, the nature of the phosphonate ester group P(O)(OR^1)$_2$ can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below.

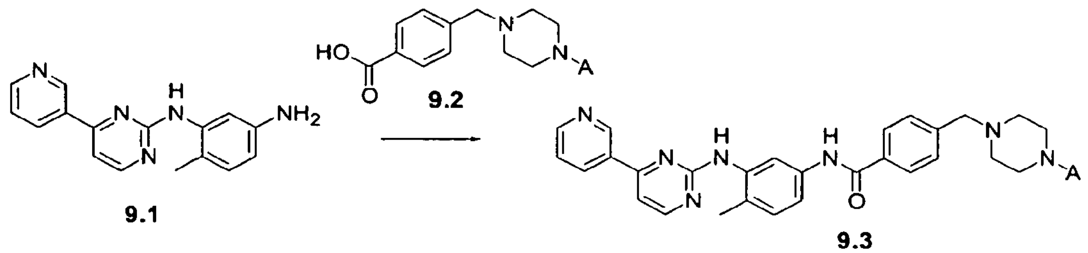
Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH], *etc.*

Example 9

Preparation of Representative Compounds of Formulae 4-7

Representative compounds of the invention can be synthesized as follows:



9.1 **9.2** **9.3**

The preparation of compounds of the invention in which A is Br, I, [SH], [NH], *etc.*, or the group link-$P(O)(OR^1)_2$ is illustrated above. Amine **9.1** is coupled with the acid **9.2** to give the amide **9.3**. The preparation of amides from carboxylic acids and derivatives is described, for example, in "Organic Functional Group Preparations," by S.R. Sandler and W. Karo, Academic Press, 1968, p. 274. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

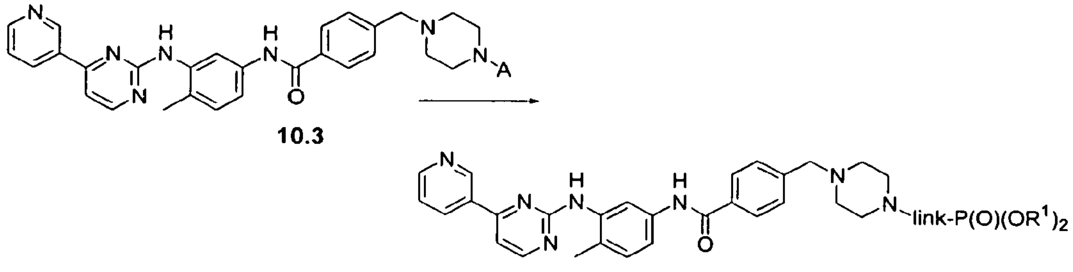
Alternatively, the carboxylic acid may first be converted into an activated derivative, such as the acid chloride or anhydride, and then reacted with the amine in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride is effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane. Preferably, the acid **9.2** is treated with oxalyl chloride in an inert solvent such as dichloromethane followed by the addition of a few drops of DMF and then treated with the amine **9.1** to give the amide **9.3**. The acid, **9.2** is prepared according to the methods described herein.

Example 10

Synthesis of Representative Compounds of Formulae 4-7

Preparations of representative compounds of the invention can be made as follows:



10.3

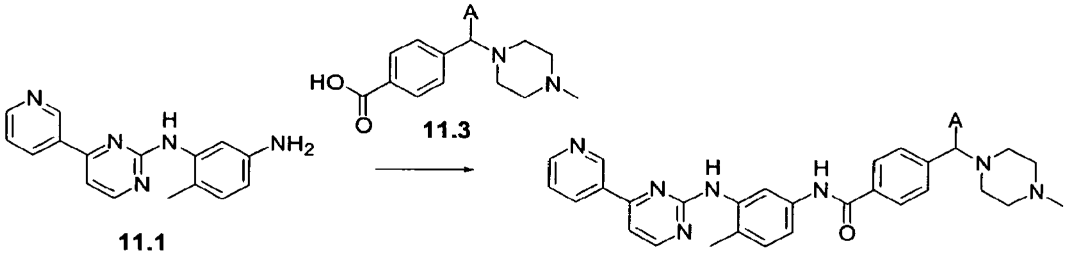
10.4

The reactions shown in Example 9 illustrate the preparation of the compounds **10.3** in which the substituent A is either the group link-P(O)$(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br, *etc.* The conversion of the compounds **10.3** in which A is [OH], [SH], [NH], Br, *etc.*, into the phosphonate esters **10.4** is described herein. In this procedure, the compounds **10.3** are converted, using the procedures described hereinbelow, into the compounds **10.4**.

Example 11

Synthesis of Representative Compounds of Formulae 4-7

Preparations of representative compounds of Formulae 4-7 can be made as follows:



11.1

11.3

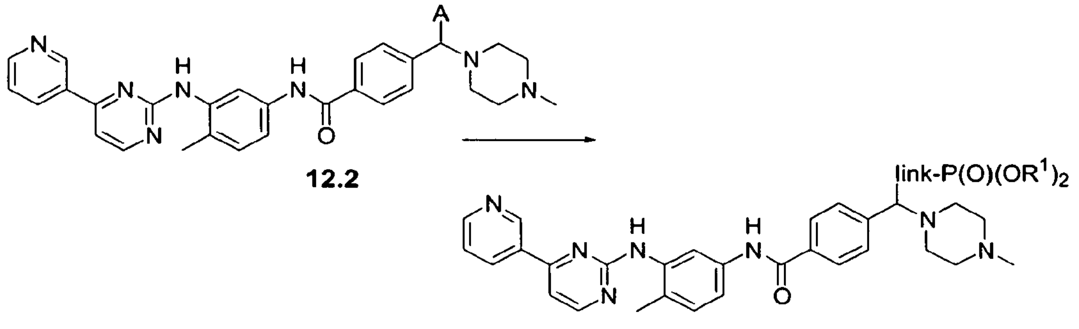
11.2

The preparation of representative compounds of the invention in which A is Br, I, [SH], [NH], *etc.*, or the group link-P(O)$(OR^1)_2$ is illustrated. The amine **11.1** is treated with acid **11.3** as described above to give the amide **11.2**. The preparation of acid **11.3** is described hereinbelow.

Example 12

Synthesis of Representative Compounds of Formulae 4-7

Preparations of representative compounds of the invention can be made as follows:



12.2

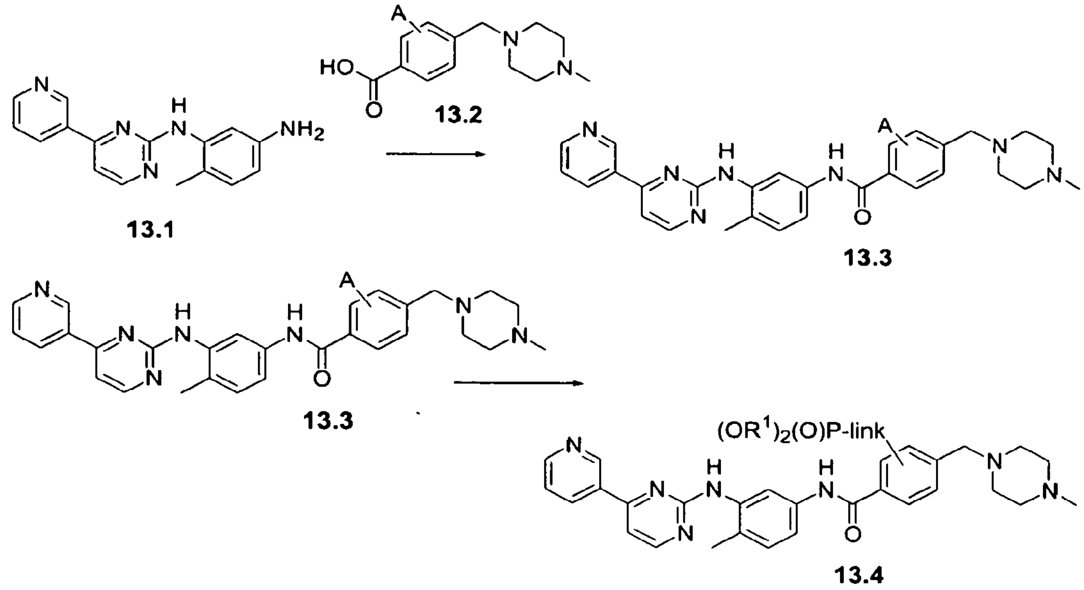
12.3

The reactions shown in Example 11 illustrate the preparation of the compounds of the invention in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br, *etc.* The conversion of the compounds **12.2** in which A is [OH], [SH], [NH], Br, *etc.*, into the phosphonate esters **12.3** is described herein. In this procedure, the compounds **12.2** are converted, using the procedures described below, into the compounds **12.3**.

Example 13

Synthesis of Representative Compounds of Formulae 4-7

Preparations of representative compounds of Formulae 4-7 can be made as follows:



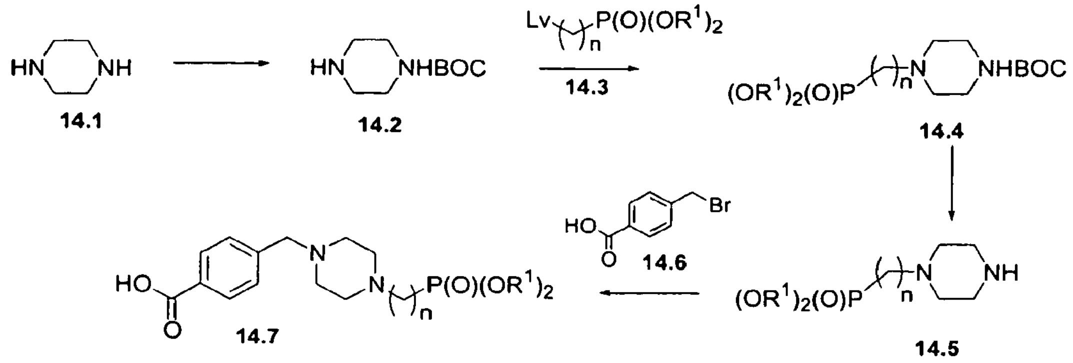
The preparation of compounds of the invention in which A is Br, I, [SH], [NH], *etc.*, or the group link-P(O)(OR^1)$_2$. The amine **13.1** is treated with acid **13.2** as described above, to give the amide **13.3**. The preparation of acid **13.2** is described below.

The reactions shown above illustrate the preparation of the compounds **13.3** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br, *etc.* The conversion of the compounds **13.3** in which A is [OH], [SH], [NH], Br, *etc.*, into the phosphonate esters **13.4**. In this procedure, the compounds **13.3** are converted, using the procedures described below is also shown above.

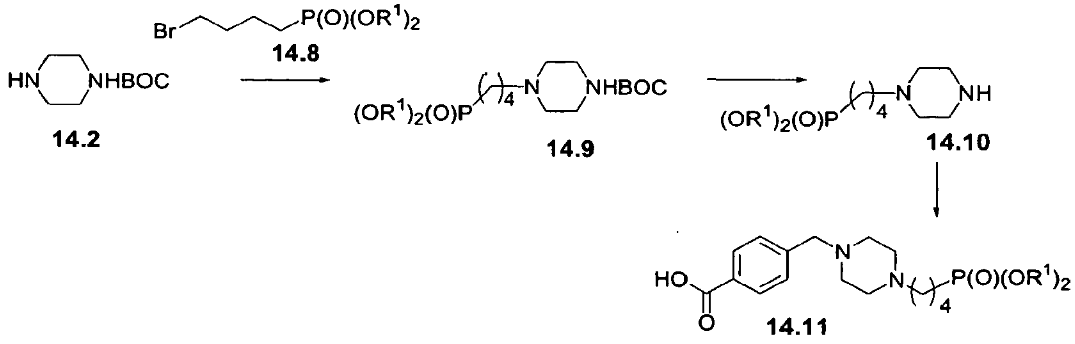
Example 14

Preparation of Representative Compounds of Formulae 4-7

The preparation of phosphonate-containing derivatives of compounds of the invention in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR^1)$_2$ that are employed in the preparation of the phosphonate ester intermediates of the invention is illustrated below.


14.1
14.2
Lv P(O)(OR¹)₂ n
14.3
14.4
14.5
14.6
14.7
HN NH
HN NHBOC
(OR¹)₂(O)P n N NHBOC
(OR¹)₂(O)P n N NH
HO O Br
HO O N N P(O)(OR¹)₂ n

Piperazine **14.1** is protected with a BOC group according to methods described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p. 518ff. In one embodiment, piperazine is treated with 1 equivalent of BOC anhydride in methanol or DMF and one equivalent of triethylamine to give the BOC amine **14.2**. Treatment of **14.2** with an alkylphosphonate **14.3** in which Lv is a leaving group such as triflate, Br, Cl, Mesyl, *etc.*, in the presence of a suitable base, affords the product **14.4**. The base required for this transformation is typically an inorganic base such as, for example, potassium carbonate, in the presence of an organic solvent such as dimethylformamide. The reaction proceeds at from ambient temperature to about 80° to afford the displacement products **14.4**. Deprotection, of the BOC-amine group as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p520ff, affords the amine **14.5**. The amine **14.5** is then reacted with the acid **14.6** (Aldrich) in the presence of a base to give the product acid **14.7**.

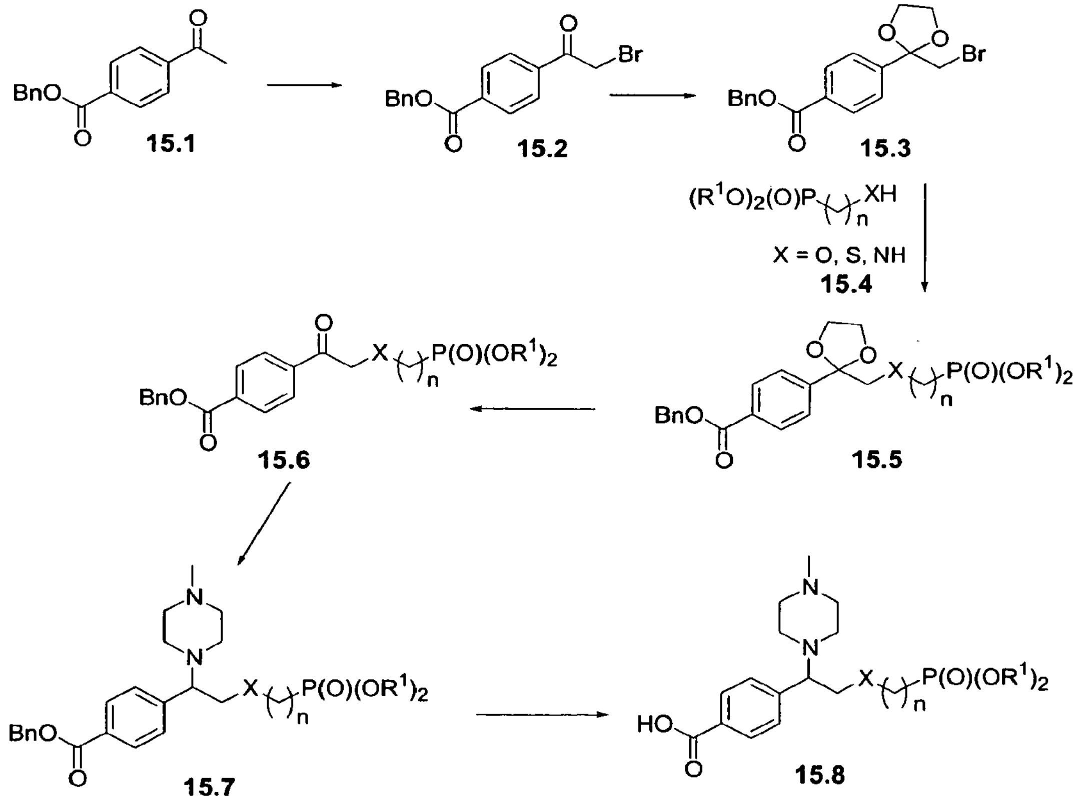

Br P(O)(OR¹)₂
14.8
HN NHBOC
14.2
(OR¹)₂(O)P 4 N NHBOC
14.9
(OR¹)₂(O)P 4 N NH
14.10
HO O N N P(O)(OR¹)₂ 4
14.11

For example, as illustrated above, **14.2** prepared from piperazine as described above, is treated with bromophosphonate **14.8**, prepared as described in Syn, 9:909 (1999), and potassium carbonate in THF to give the amine **14.9**. The BOC amine **14.9** is then deprotected by treatment with trifluoroacetic acid in dichloromethane to give the amine **14.10**. The amine **14.10** is then reacted with the bromomethyl benzoic acid **14.6** in THF or dioxane in the presence of triethylamine, or aqueous potassium carbonate, to give the acid **14.11**. Using the above procedures, but employing, in place of the bromo phosphonate compound **14.8**, different phosphonates **14.3**, the corresponding products **14.7** are obtained.

Example 15

Synthesis of Representative Compounds of Formulae 4-7

Preparations of representative compounds of the invention can be made as follows:

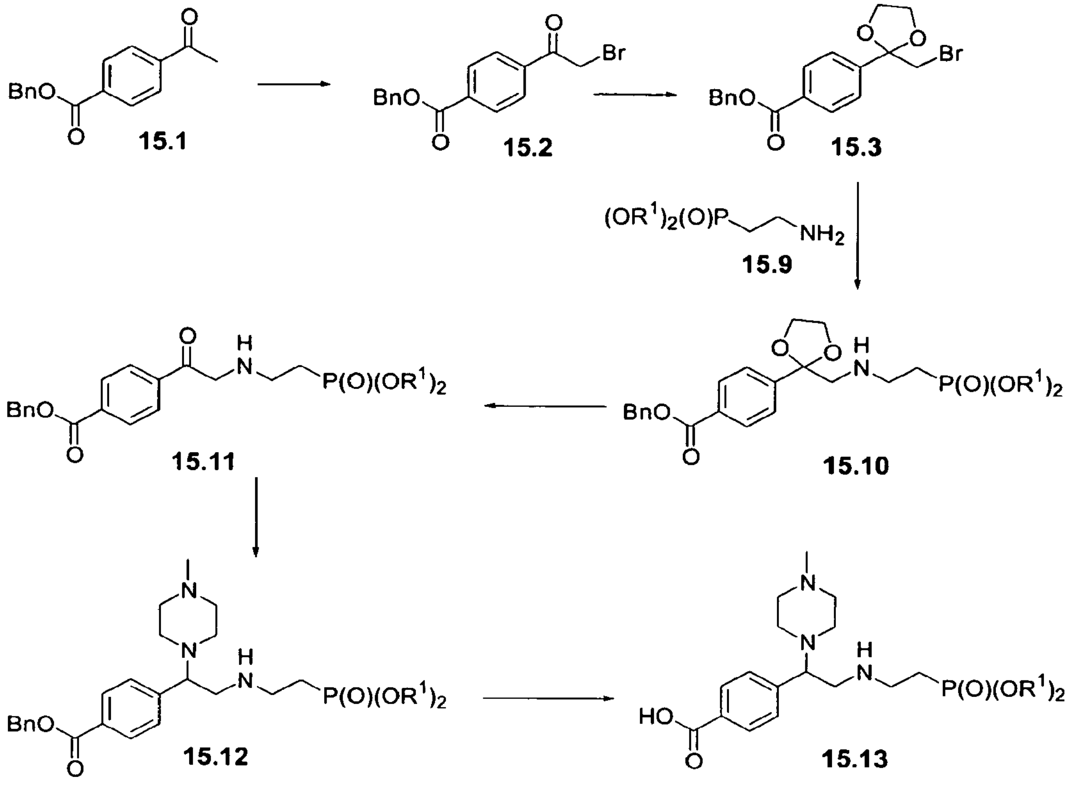


The preparation of acids of the compounds of the invention in which the phosphonate is attached to the scaffold through a heteroatom and carbon linker is shown below. The benzyl protected ketone **15.1**, prepared from the corresponding acid by treatment with benzyl alcohol in the presence of DCC and DMAP in DMF, as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p. 373ff., is treated with a brominating agent to give the bromo ketone **15.2**.

Protection of the ketone as the cyclic dioxalone as described at p. 312ff in "Ptorective Groups in Organic Synthesis" gives **15.3**. Dioxalone **15.3** is then treated with the dialkyl hydroxy, thio or amino-substituted alkylphosphonate **15.4** to give the dioxalone **15.5**. The reaction is performed in the presence of a base, in a polar aprotic solvent such as dioxane or N-methylpyrrolidinone. The base employed in the reaction depends on the nature of the reactant **15.4**. For example, if X is O, a strong base such as, for example, lithium hexamethyldisilylazide or potassium tert. butoxide is employed. If X is S, NH or N-alkyl, an inorganic base such as cesium carbonate and the like is employed. Deprotection of the dioxalone as described at p. 317ff of "Protective Groups in Organic Synthesis," gives ketone **15.6.** Ketone **17.6** is then treated under reductive amination conditions with N-methyl piperazine to give the amine **15.7**.

The preparation of amines by means of reductive amination procedures is described, for example, in "Comprehensive Organic Transformations," by R. C. Larock, 2nd edition, p. 835. In this procedure, the amine component and the aldehyde component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride or diisobutylaluminum hydride, to yield the amine product.

Deprotection of the ester group as described at p. 373ff of "Protective Groups in Organic Synthesis" then affords the acid **15.8**.



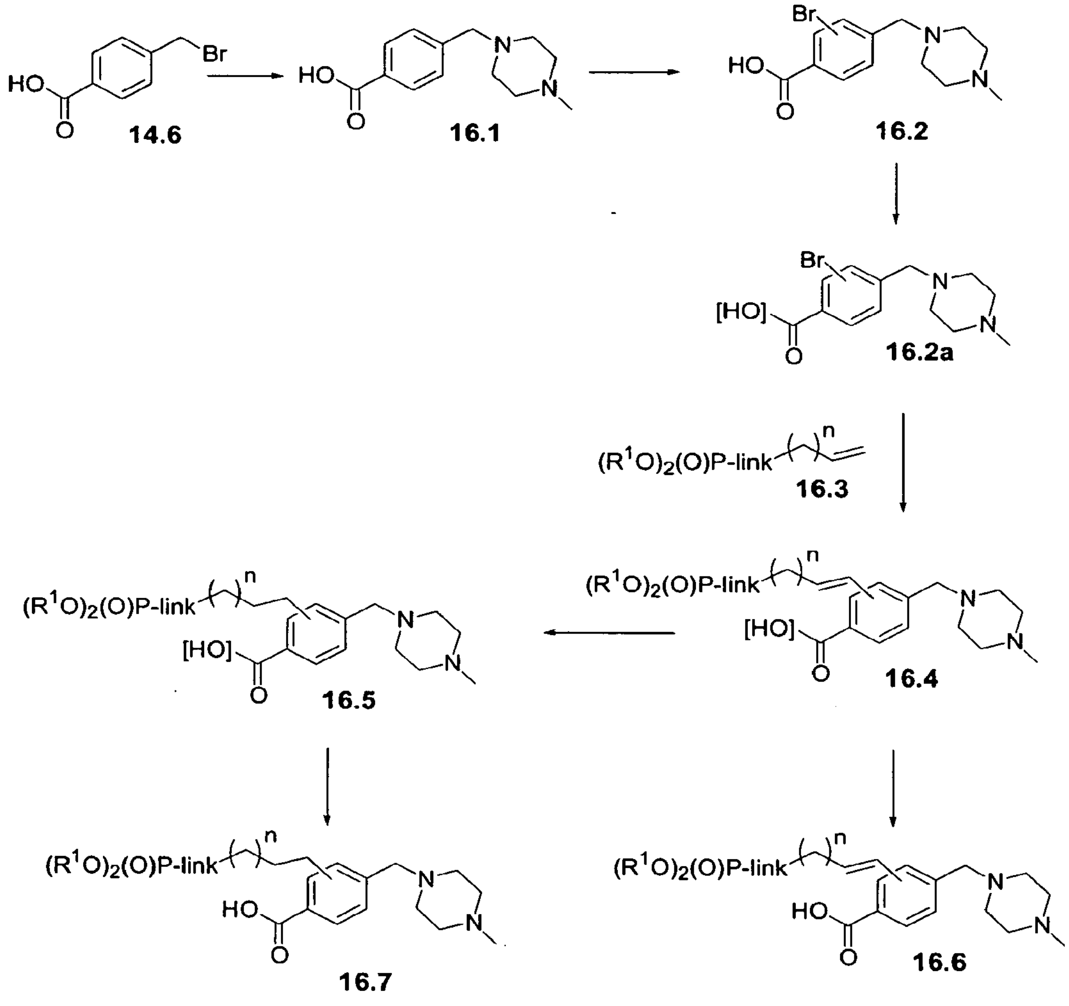
For example, the preparation of a specific compound of the invention is shown above. 4-acetyl benzoic acid is treated with benzyl bromide in the presence of potassium carbonate in aqueous THF to give the ester **15.1**. Treatment of the ester **15.1** with bromine in acetic acid, or NBS and AIBN in CCl_4 affords the bromide **15.2**. Bromide **15.2** is then reacted with 1,2-ethane diol in toluene at reflux under a dean stark head with a catalytic amount of p-TsOH present to give the dioxalone **15.3**. Dioxalone **15.3** is reacted with dialkyl 2-aminoethyl phosphonate **15.9**, prepared as described in J. Org. Chem., 65:676 (2000), in dimethylformamide at ca 80°, in the presence of potassium carbonate, to afford the amine **15.10**. Treatment of the dioxalone **15.10** with 1N hydrochloric acid in THF then yields the ketone **15.11**. Ketone **15.11** is reacted with N-methyl piperazine in the presence of triethylamine followed 30 minutes later by the addition of sodiumcyano borohydride to give the amine **15.12**. Removal of the benzyl ester by hydrolysis using sodium hydroxide in aqueous THF gives the acid **15.13**.

Using the above procedures, but employing, in place of the amino phosphonate compound **15.9**, different phosphonates **15.4**, the corresponding products **15.8** are obtained.

Example 16

Synthesis of Representative Compounds of Formulae 4-7

Preparations of representative compounds of the invention can be made as follows:

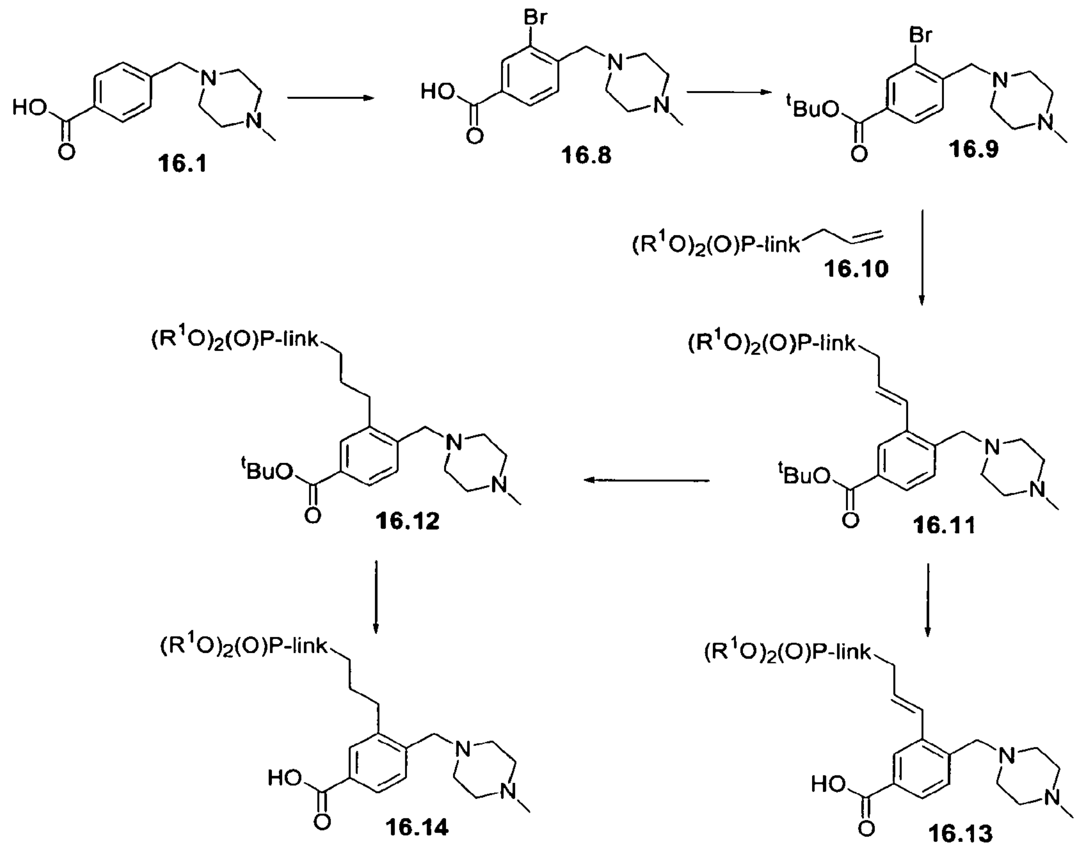


The preparation of an acid of the invention in which the phosphonate is attached through a unsaturated or saturated carbon linker, is shown above. In this procedure, the acid **14.6** (Aldrich) is treated with N-methyl piperazine as described in Example 14 for the preparation of **14.7**, to give the acid **16.1**. Acid

16.1 is then brominated with bromine or NBS to give the bromide **16.2**. Bromide **16.2** is optionally protected as the benzyl or t-butyl ester, as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p373ff to give **16.2a.**

Ester **16.2a** is then coupled, by means of a palladium-catalyzed Heck reaction with a dialkyl alkenyl phosphonate **16.3,** to afford the coupled product **16.4**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in "Advanced Organic Chemistry," by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12:146 (1979). The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxane, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product **16.4**. Optionally, the product **16.4** can be reduced to afford the saturated phosphonate **16.5**. Methods for the reduction of carbon-carbon double bonds are described, for example, in "Comprehensive Organic Transformations," by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction, and chemical reduction, the latter for example employing diborane or diimide.

For example, the preparation of a specific compound of the invention is illustrated below.

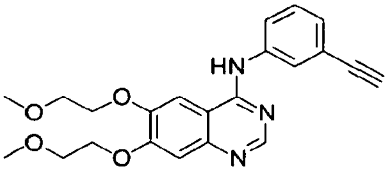


Amine **16.1** is then treated with NBS and AIBN in carbon tetrachloromethane at reflux to give the bromide **16.8**. Bromide **16.8** is then reacted in t-butanol with DCC and DMAP to give the t-butyl ester **16.9**. Ester **16.9** is then reacted with dialkyl propenyl phosphonate **16.10**, the preparation of which is described in J. Med. Chem., 39:949 (1996), in the presence of bis(triphenylphosphine) palladium(II) chloride , as described in J. Med. Chem., 35:1371 (1992), to afford the coupled product **16.11**. This product **16.11** is then treated with aqueous HCl in dioxane to give the acid **16.13**. Optionally, the alkene **16.11** can be reduced by reaction with diimide, as described in J. Org. Chem., 30:3965 (1965), to afford the saturated product **16.12**. Hydrolysis of the ester as described above through treatment with aqueous HCl in dioxane gives the acid **16.14**.

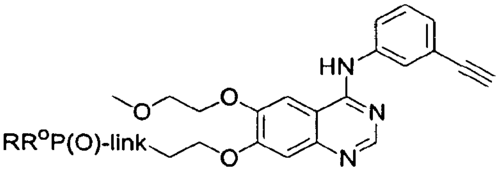
Using the above procedures, but employing, in place of the phosphonate compound **16.10**, different phosphonates **16.3**, the corresponding products **16.6** and **16.7** are obtained.

Examples 17-26

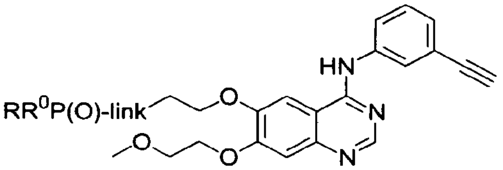
Preparation of Representative Compounds of Formulae 8-11



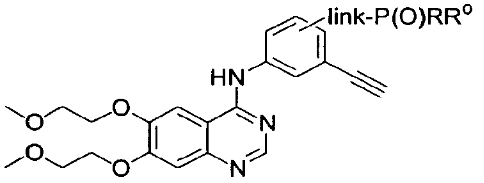
Erlotinib
EP 0817775 B1



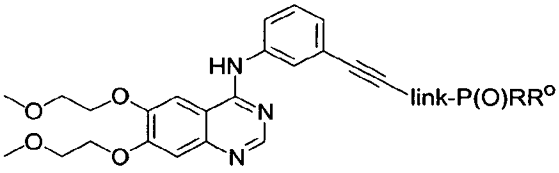
17.1a



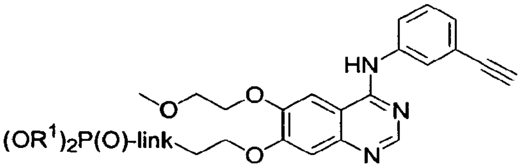
17.2a



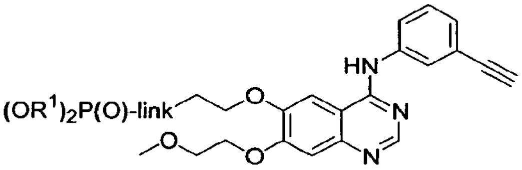
17.3a



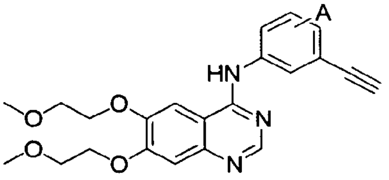
17.4a


(OR^1)2P(O)-link

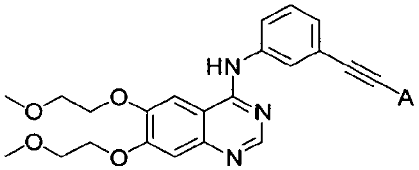
17.1


(OR^1)2P(O)-link

17.2

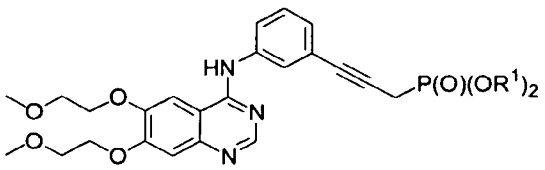


17.3

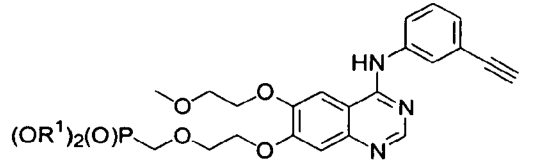


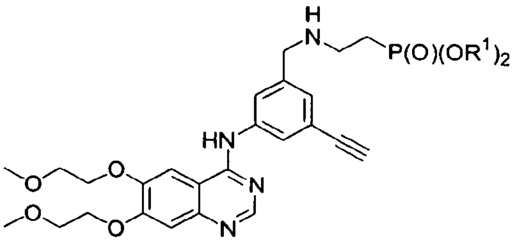
17.4

Carbon



Heteroatom linked





Representative compounds of the invention, *e.g.*, as shown above, can be synthesized according to the following methods.

Phosphonate Interconversions

The final compounds described above are synthesized according to the methods described herein. The intermediate phosphonate esters are shown above (**17.1**, **17.2**, **17.3** and **17.4**) and these compounds can be used to prepare the final compounds above (**17.1a**, **17.2a**, **17.3a** and **17.4a**), by one skilled in the art, using known methods for synthesis of substituted phosphonates. These methods are similar to those described for the synthesis of amides. The preparation of amides from carboxylic acids and derivatives is described, for example, in "Organic Functional Group Preparations," by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274. Further methods are described below for the synthesis of the phosphonate diesters and can in some cases be applied to the synthesis of phosphor-amides.

In the following schemes, the conversion of various substituents into the group link-$P(O)(OR^1)_2$, where R^1 is defined above, or indeed the final stage of $P(O)RR^o$, as defined above, can be effected at any convenient stage of the synthetic sequence, or in the final step. The selection of an appropriate step for the introduction of the phosphonate substituent is made after consideration of the chemical procedures required, and the stability of the substrates to those procedures. It may be necessary to protect reactive groups, for example hydroxyl, amino, during the introduction of the group link-$P(O)(OR^1)_2$ or $P(O)RR^o$

In the succeeding examples, the nature of the phosphonate ester group $P(O)(OR^1)_2$ can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below.

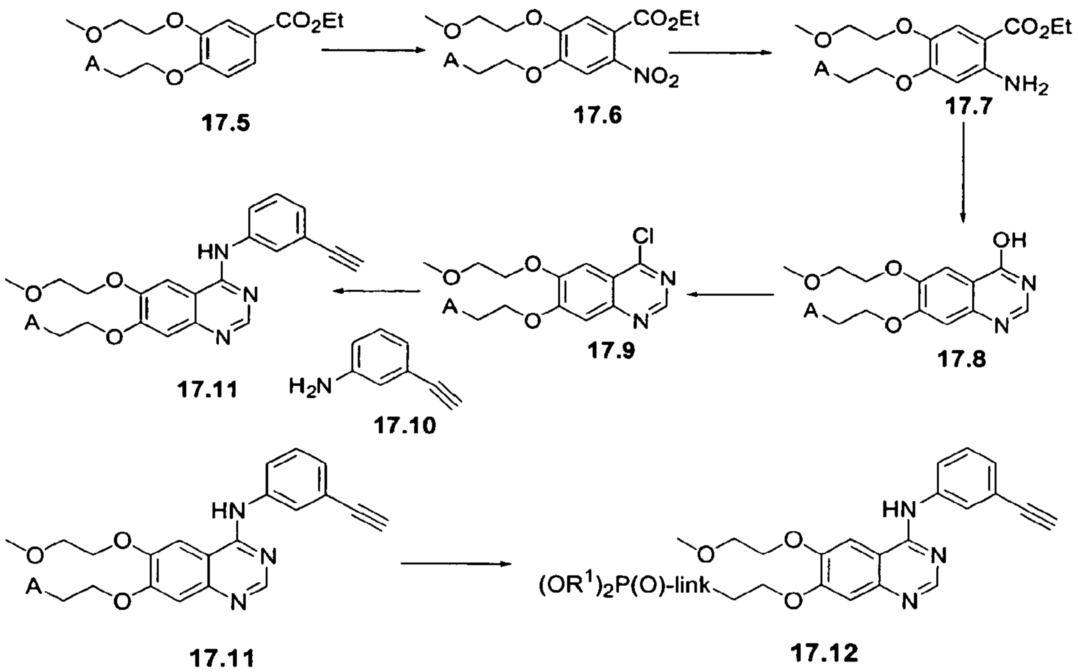
Protection of reactive substituents.

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999. Reactive substituents which may be protected are shown in the accompanying schemes as, for example, [OH], [SH], *etc.*

The procedures described in Examples 17-26 for the introduction of phosphonate moieties are, with appropriate modifications known to one skilled in the art, transferable to different chemical substrates. Thus, for example, the methods described herein for the introduction of phosphonate groups onto the aryl ring of **25.6** are also applicable to theintroduction of phosphonate moieties onto the alkyne **26.8**, and the reverse is also true.

Example 17

Preparation of Representative Compounds of Formulae 8-11



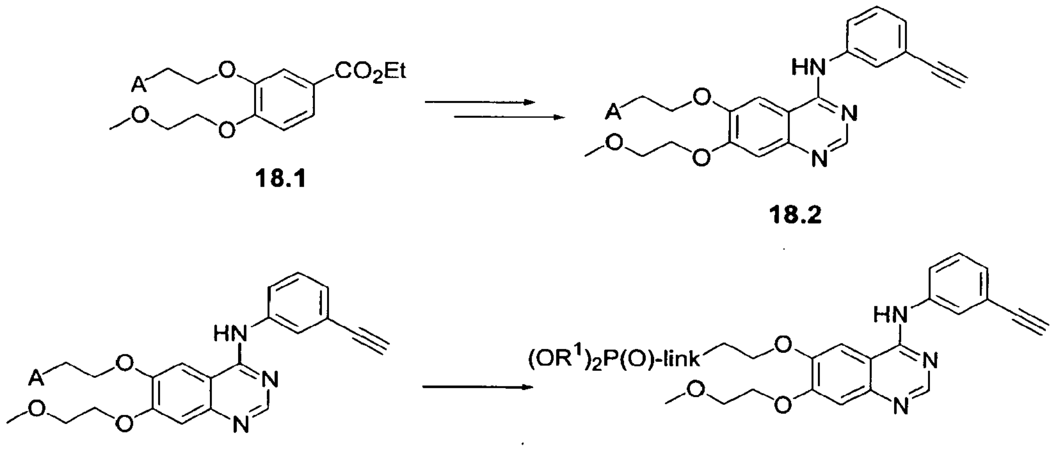
Illustrated above is the synthesis of target molecules of the invention, in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR^1)$_2$. The preparation of **17.5** in which is A is a phosphonate is described below. Conversion of **17.5** into **17.11** in which A is methoxymethyl is described in EP 0817775 B1 and similar conditions are used to convert **17.5** to **17.11** in which A is the group link-P(O)(OR^1)$_2$. Nitration of the diether **17.5** gives nitro compound **7.6**, which, followed by reduction under standard reducing conditions as described in "Comprehensive Organic Transformations," by R. C. Larock, 2nd Edition, 1999, p821, affords the amine **17.7**. For example, **17.5** is treated with cold nitric acid in acetic acid, followed by catalytic hydrogenolysis of the nitro product in acidic ethanol over platinum oxide at high pressure to give the amine **17.7**. The hydrochloride salt that is isolated is then heated at ca 160°C with ammonium formate and formamide to generate the quinazoline **17.8**. The quianzoline is converted to the chloride, **17.9**, as described in EP 0817775 B1. In one embodiment, the quinazoline **17.8** is treated with oxalyl chloride in chloroform and DMF to give the chloride **17.9**. Displacement of the chloride by the amine,

17.10, then affords the product **17.11**. For example, heating the chloride **17.9** with 3-ethynyl-aniline in isopropanol at reflux gives **17.11**.

The reactions shown above illustrate the preparation of the compounds **17.11** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br, *etc.* The conversion of the compounds **17.11** in which A is [OH], [SH], [NH], Br, *etc.*, into the phosphonate esters **17.12** is also depicted above. In this procedure, the compounds **17.11** are converted, using the procedures described in Examples 17-26 into the compounds **17.12**.

Example 18

Preparation of Representative Compounds of Formulae 8-11



18.1

18.2

18.2

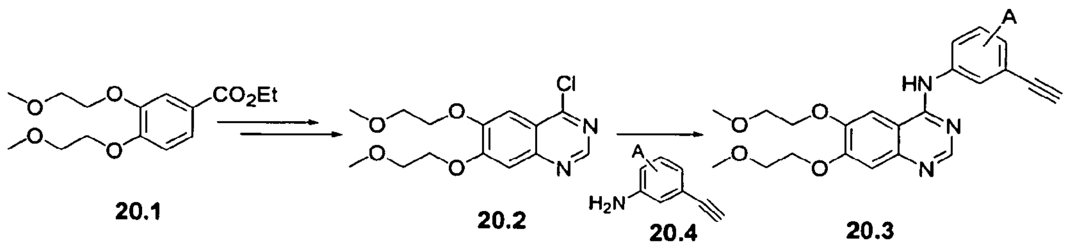
18.3

Illustrated above is the synthesis of target molecules of the invention in which A is Br, Cl, [OH], [NH], or the group link-$P(O)(OR^1)_2$. Conversion of **18.1** into **18.2** is completed using the conditions described above in Example 17 for the conversion of **17.5** into **17.11**. The preparation of **18.1** in which is A is a phosphonate is described below in Example 23.

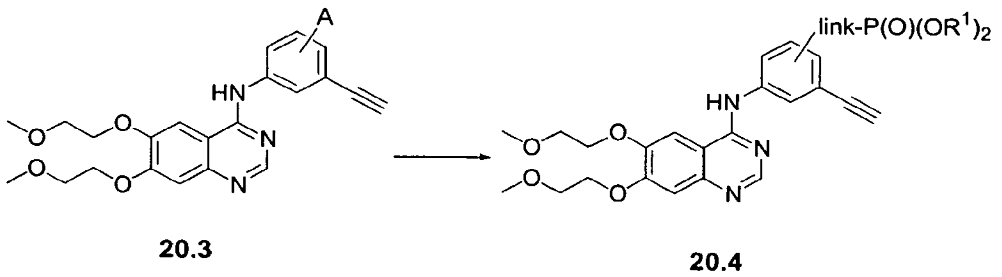
The reactions shown above illustrate the preparation of the compounds **18.2** in which the substituent A is either the group link-$P(O)(OR^1)_2$ or a precursor such as [OH], [SH], [NH], Br, *etc.* Also depicted above is the conversion of the compounds **18.2** in which A is [OH], [SH], [NH], Br, *etc.*, into the phosphonate esters **18.3**. In this procedure, the compounds **18.2** are converted, using the procedures described herein into the compounds **18.3.**

Example 20

Preparation of Representative Compounds of Formulae 8-11



20.1 **20.2** **20.4** **20.3**



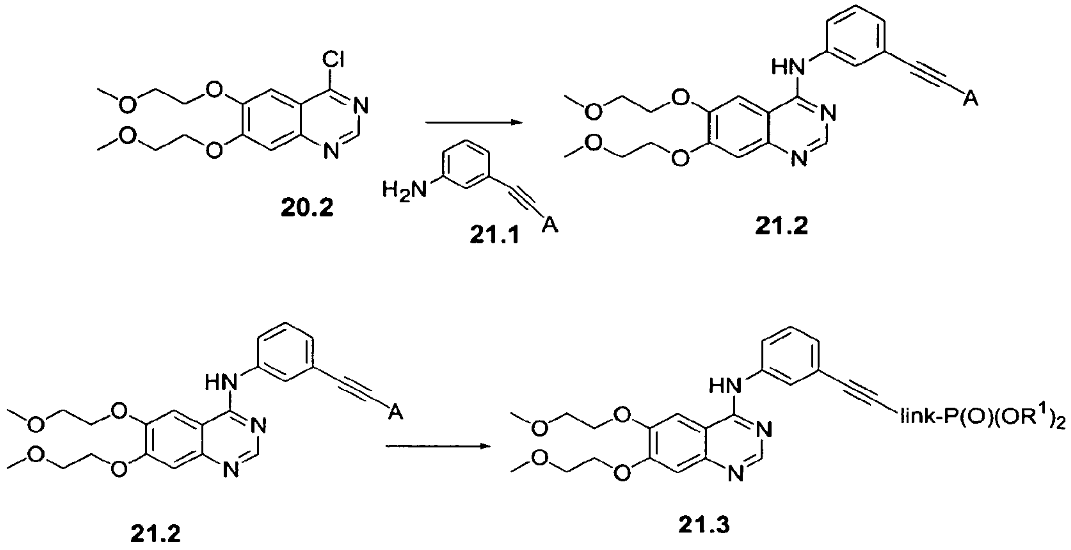
20.3 **20.4**

Illustrated above is the synthesis of target molecules of the invention, in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR^1)$_2$. The preparation of **20.1** is described in EP 0817775 B1 . Diether **20.1** is converted to the chloride **20.2** using conditions described in EP 0817775 B1 or as described in Example 17. Treatment of chloride **20.2** with amine **20.4** in refluxing isopropanol gives **20.3**. The preparation of **20.4** in which A is group link-P(O)(OR^1)$_2$ is shown in Example 25.

The reactions shown above illustrate the preparation of the compounds **20.3** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br, *etc.* Also depicted above is the conversion of the compounds **20.3** in which A is [OH], [SH], [NH], Br, *etc.*, into the phosphonate esters **20.4**. In this procedure, the compounds **20.3** are converted, using the procedures described in Examples 17-26, into the compounds **20.4**.

Example 21

Preparation of Representative Compounds of Formulae 8-11

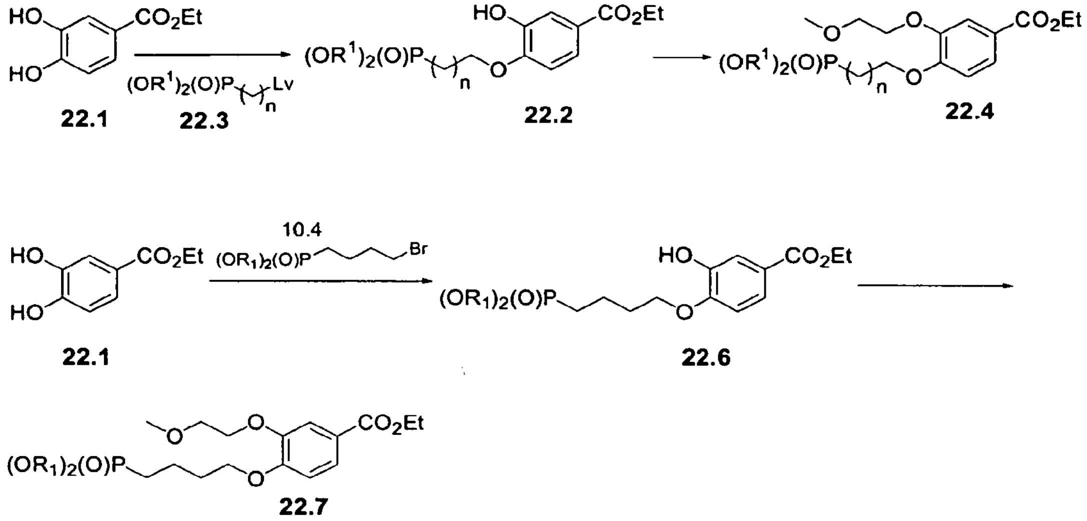


Illustrated above is the synthesis of target molecules of the invention, in which A is Br, Cl, [OH], [NH], or the group link-P(O)(OR^1)$_2$. The preparation of **20.2** is described in Example 20. Chloride **20.2** is converted to the amine **21.2** by treatment with amine **21.1** in refluxing isopropanol. The preparation of **21.1** in which A is group link-P(O)(OR^1)$_2$ is shown in Example 26.

The reactions shown above illustrate the preparation of the compounds **21.2** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br, *etc.* Also depicted above is the conversion of the compounds **21.2** in which A is [OH], [SH], [NH], Br, *etc.*, into the phosphonate esters **21.3**. In this procedure, the compounds **21.2** are converted, using the procedures described in Examples 17-26, into the compounds **21.3**.

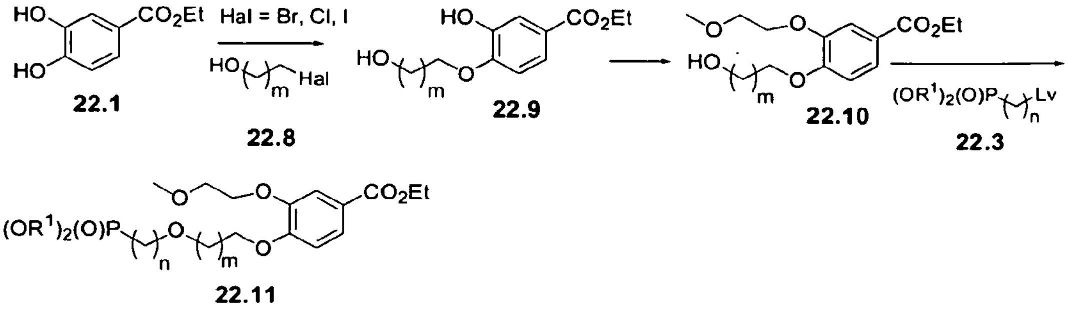
Example 22

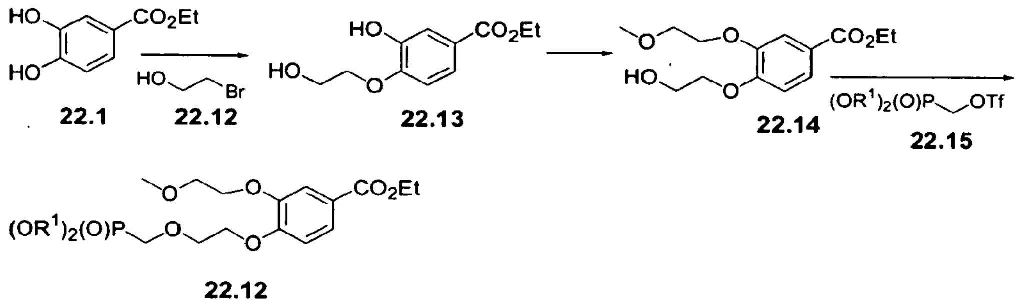
Preparation of Representative Compounds of Formulae 8-11



Described herein is the preparation of phosphonate-containing derivatives **22.11** and **22.12** that are employed in the preparation of the phosphonate ester intermediates **17.1.** The dihydroxybenzoic acid **22.1** is treated with one equivalent of the phosphonate alkylating agent, in which Lv is a leaving group such as mesyl, trifluoromethanesulfonyl, Br, I, Cl, tosyl, *etc.*, in the presence of base as described in EP 0817775 B1, to give the ether **22.2.** The ether is then subjected to the same alkylating conditions in the presence of 2-bromoethylmethyl ether (Aldrich) to give the diether **12.12.**

For example, as shown above, ester **22.1,** prepared from the corresponding acid (Aldrich) by refluxing in concentrated HCl and ethanol, in acetone is treated with dialkyl 4-bromobutylphosphonate **22.4,** prepared as described in Syn, 9:909 (1999), potassium carbonate and tetrabutylammonium iodide to give the ether **22.6.** Ether **22.6** is then treated with 2-bromoethylmethyl ether (Aldrich), potassium carbonate and tetrabutyl ammonium iodide to give the diether **22.7.** Using the above procedures, but employing, in place of the bromobutylphosphonate **22.5,** different phosphonates **22.3,** the corresponding products are obtained.



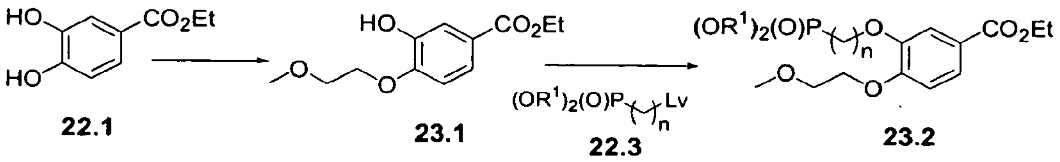


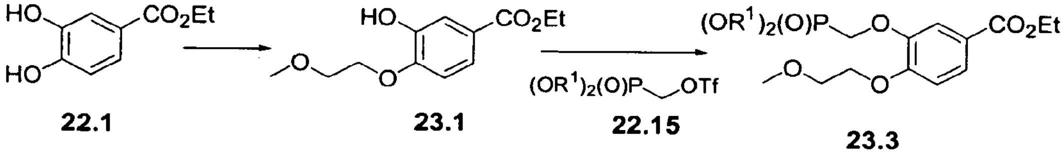
The preparation of phosphonate-containing derivatives **22.11** and **22.12** is shown above. The dihydroxybenzoic acid **22.1** is treated with one equivalent of alcohol **22.8** as described above to give ether **22.9**. This ether **22.9** is then further treated with one equivalent of 2-bromoethylmethyl ether (Aldrich), and one equivalent of base as described above to give the diether **22.10**. Treatment, once again with an phosphonate alkylating agent **22.3**, in which Lv is a group such as mesyl, trifluoromethanesulfonyl, Br, I, Cl, tosyl, *etc.*, in the presence of base then affords ether **22.11**.

For example, **22.1** in acetone is treated with 2-bromoethanol, as described above for the preparation of **22.2** from **22.1**, to give **22.13**. Reaction with 2-bromoethylmethyl ether (Aldrich), and one equivalent of sodium hydride in DMF, then affords the diether **22.14**. Reaction of diether **22.14** with triflate **22.15**, prepared as described in Tet. Lett., 27:1497 (1986), and potassium carbonate in DMF, gives the ether **22.12**. Using the above procedures, but employing, in place of the bromobutylphosphonate **22.15**, different phosphonates **22.3**, and in place of alcohol **22.12**, different alcohols **22.8**, the corresponding products are obtained.

Example 23

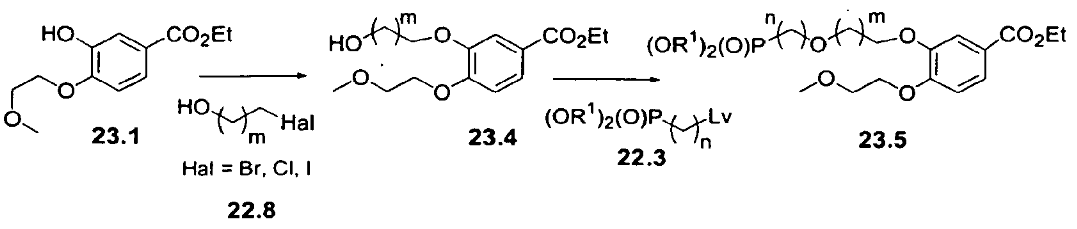
Preparation of Representative Compounds of Formulae 8-11

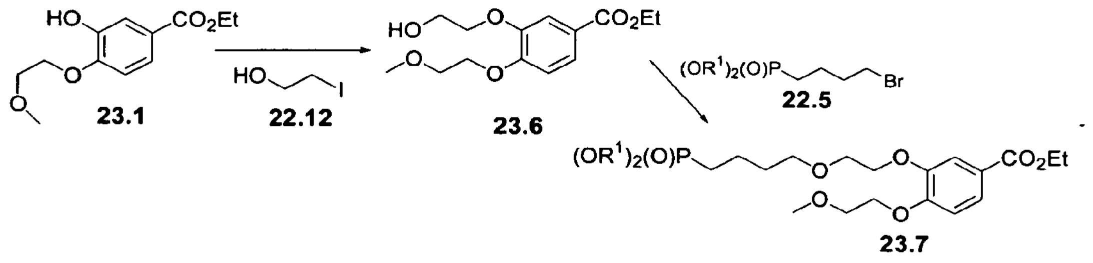




Described above is the preparation of phosphonate-containing derivatives of compounds of the invention that are employed in the preparation of the phosphonate ester intermediates **17.2**. The dihydroxybenzoic acid **22.1** is first treated with 2-bromoethylmethyl ether (Aldrich), as described in Example 22, to give the ether **23.1**. Ether **23.1** is then treated with one equivalent of the phosphonate alkylating agent, in which Lv is a group such as mesyl, trifluoromethanesulfonyl, Br, I, Cl, tosyl, *etc.*, in the presence of base, as described in EP 0817775 B1, to give the ether **23.2**. For example, as shown above, ether **23.1** is treated with triflate **22.15**, prepared as described in Tet. Lett., 27:1497 (1986), and potassium carbonate in DMF, to give the ether **23.3**.

Using the above procedures, but employing in place of the phosphonate **22.5** different phosphonates **22.3**, the corresponding products **23.2** are obtained.





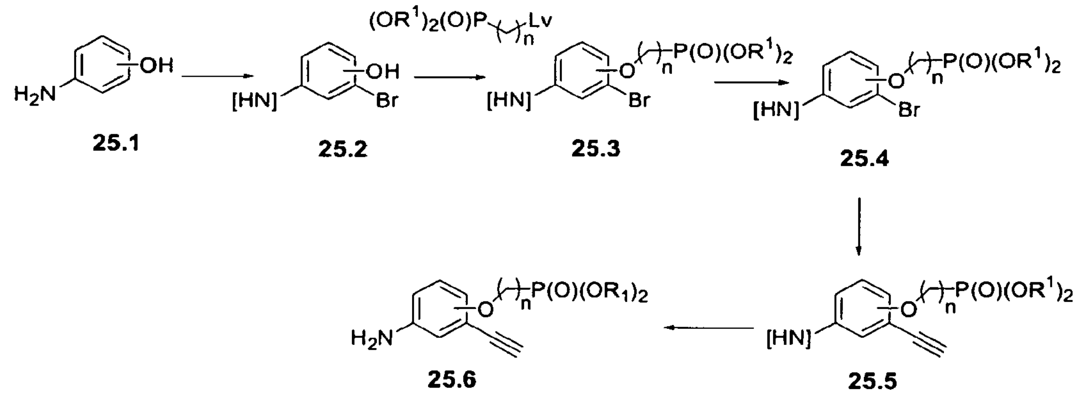
Described above is the preparation of phosphonate-containing derivatives **23.5** that are employed in the preparation of the phosphonate ester intermediates **17.1.** Ether **23.1** is reacted with 2-bromoethanol, as described in Example 22 for the preparation of **23.2** from **22.1**, to give **23.4.** Treatment of diether **23.4** with a phosphonate alkylating agent **22.3**, in which Lv is a group such as mesyl, trifluoromethanesulfonyl, Br, I, Cl, tosyl, *etc.*, in the presence of base then affords ether **23.5**.

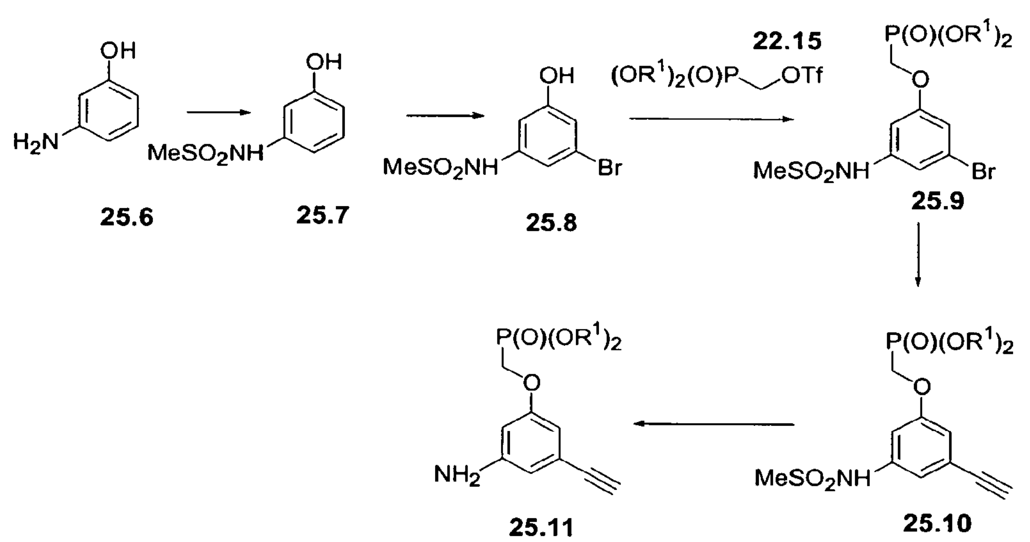
For example, **23.1** in acetone is treated 2-bromoethanol, **22.1**, as described in Example 22 for the preparation of **22.2** from **22.1**, to give **23.6.** Reaction with bromobutylphosphonate **22.5**, as described above then affords **23.7**.

Using the above procedures, but employing, in place of the bromobutylphosphonate **22.5**, different phosphonates **22.3**, and in place of alcohol **22.12**, different alcohols **22.8,** the corresponding products **23.5** are obtained.

Example 25

Preparation of Representative Compounds of Formulae 8-11





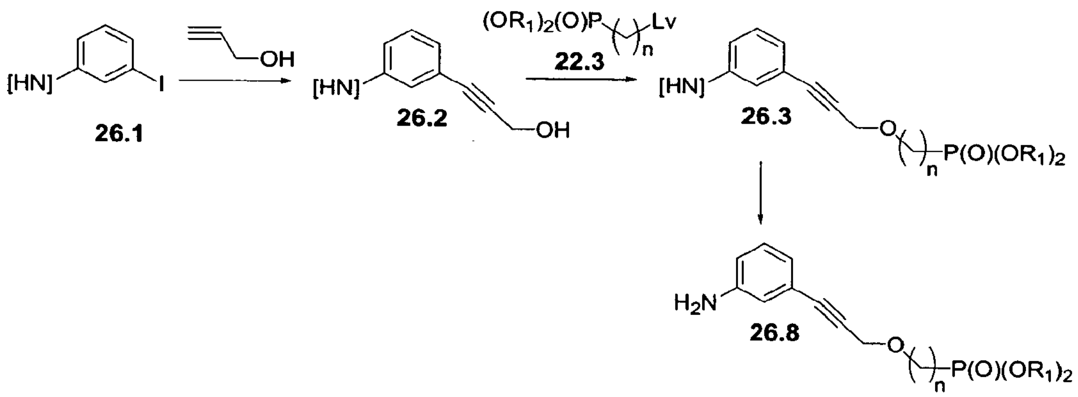
The preparation of phosphonate-containing derivatives is depicted above. Aniline **25.1** is first protected using methods described in “Protective Groups in Organic Synthesis,” by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 ch 7. Bromination of **25.2** by treatment with bromine in acetic acid or NBS in tetrachloromethane at reflux, in the presence of AIBN then affords the bromophenol **25.3**. Alkylation with a phosphonate alkylating agent **22.3** as described in Example 22 then affords the phosphonate **25.4**. Coupling with TMS acetylene by palladium mediated reaction affords the alkyne **25.5** which can then be deprotected using conditions described in “Protective Groups in

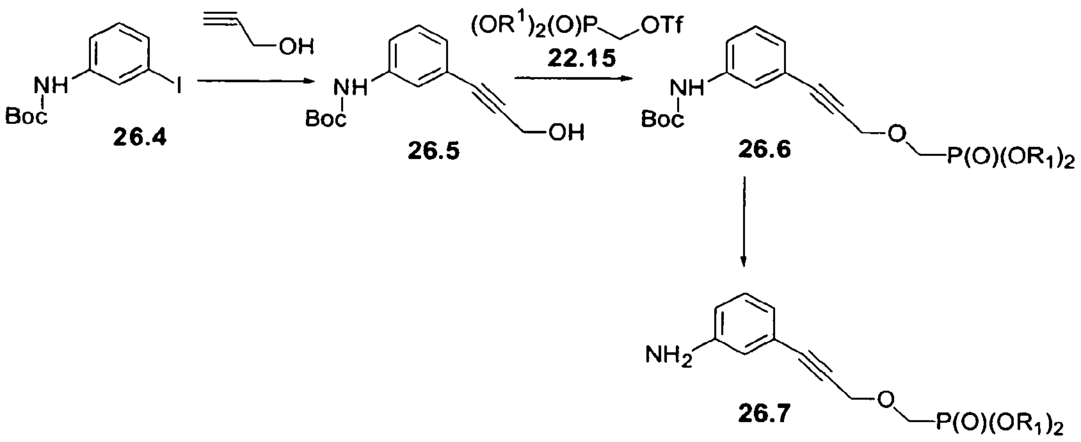
Organic Synthesis," by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 ch7 gives the amine **25.6**. The coupling of aryl halides with alkynes is described, for example, in "Comprehensive Organic Synthesis," Eds. Trost and Fleming, Oxford, 1991, 3, part2.4, p521.

For example, as shown above, 3-aminophenol, **25.6**, is treated with one equivalent of mesyl chloride in the presence of pyridine to afford **25.7**. The mesyl compound **25.7** is then treated with bromine in acetic acid to give the bromide **25.8**. Bromide **25.8** is alkylated with **22.15** as described in Example 23 to give the phosphonate **25.9**. Treatment of **25.9** with TMS-acetylene in a polar solvent such as dimethylformamide or acetonitrile, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate and copper (I) iodide, affords the coupled product **25.10.** Deprotection of the mesyl group by treatment with potassium hydroxide in THF and water gives the amine **25.11.** Using the above procedures, but employing, in place of the phosphonate **22.15**, different phosphonates **22.3**, and in place of alcohol **25.6**, different alcohols **25.1**, the corresponding products **25.6** are obtained.

Example 26

Preparation of Representative Compounds of Formulae 8-11





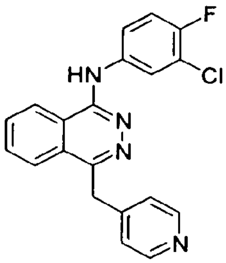
The preparation of phosphonate-containing derivatives **26.8** is shown above. 3-Iodoaniline is first protected using methods described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 ch 7. Coupling with propargyl alcohol by palladium mediated reaction, as described in Example 25 affords the alkyne **26.2**. Alkylation with a phosphonate alkylating agent **22.3** as described in Example 22 affords the phosphonate **26.3**. Finally, deprotection using conditions described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 ch7 gives the amine **26.8**. For example, 3-iodoaniline (Aldrich) is treated with BOC anhydride in the presence of pyridine and DMAP to afford **26.4**. Treatment of **26.4** with propargyl alcohol in a polar solvent such as dimethylformamide or acetonitrile, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate and copper (I) iodide, affords the coupled product **26.5**. Alkylation of **26.5** with triflate **22.15**, as described in Example 22 then affords the phosphonate **26.6**. Deprotection of the BOC group by treatment with TFA in THF or dioxane gives the amine **26.7.**

Using the above procedures, but employing, in place of the phosphonate **22.15**, different phosphonates **22.3**, and in place of iodoaniline **26.4**, different anilines, **26.1**, the corresponding products **26.8** are obtained.

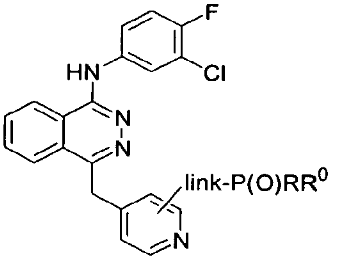
Examples 27-33

Preparation of Representative Compounds of Formulae 12-13

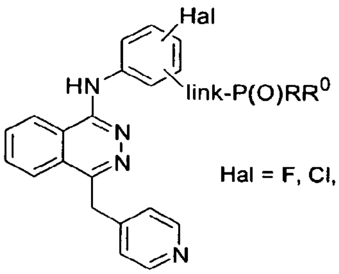
Generally, for Examples 27-33, representation compounds of the invention can be prepared as follows:



Vatalanib / PTK-787
US 6,258,812 B1

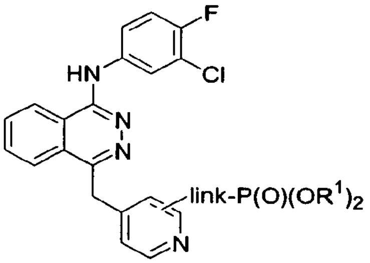


27.1a

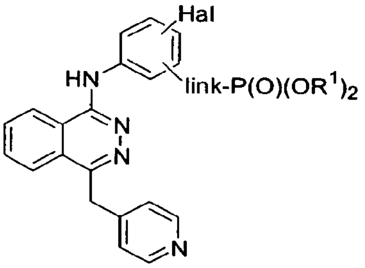


Hal = F, Cl, H

27.2a

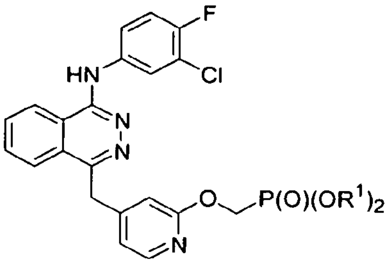


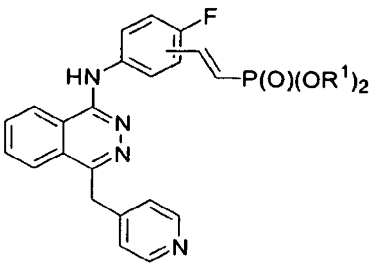
27.1

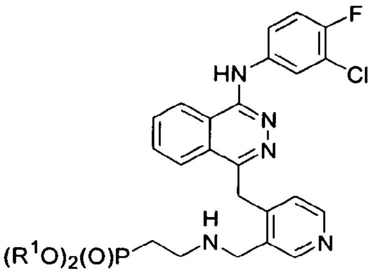


27.2

R = H, alkyl, haloalkyl, alkenyl, aralkyl, aryl.







Phosphonate Interconversions

The final compounds described above are generally synthesized according to the methods described in Examples 27-33. The intermediate phosphonate esters **27.1** and **27.2** and these compounds can be used to prepare the final compounds **27.1a** and **27.2a**, by one skilled in the art, using known methods for synthesis of substituted phosphonates. These methods are similar to those described for the synthesis of amides. The preparation of amides from carboxylic acids and derivatives is described, for example, in "Organic Functional Group Preparations," by S.R. Sandler and W. Karo, Academic Press, 1968, p. 274. Further methods are described below for the synthesis of the phosphonate diesters and can in some cases be applied to the synthesis of phosphor-amides.

In the following schemes, the conversion of various substituents into the group link-$P(O)(OR^1)_2$, where R^1 is defined as above, or indeed the final stage of $P(O)RR^o$, as defined above, can be effected at any convenient stage of the synthetic sequence, or in the final step. The selection of an appropriate step for the introduction of the phosphonate substituent is made after consideration of the chemical procedures required, and the stability of the substrates to those procedures. It may be necessary to protect reactive groups, for example hydroxyl, amino, during the introduction of the group link-$P(O)(OR^1)_2$ or $P(O)RR^o$.

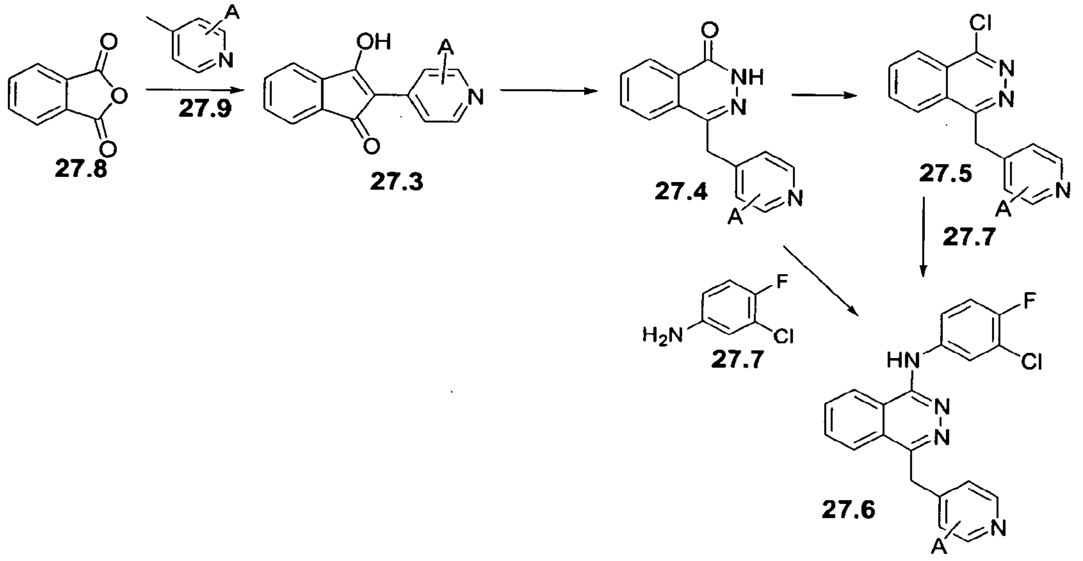
In the succeeding examples, the nature of the phosphonate ester group $P(O)(OR^1)_2$ can be varied, either before or after incorporation into the scaffold, by means of chemical transformations. The transformations, and the methods by which they are accomplished, are described below.

Protection of reactive substituents

Depending on the reaction conditions employed, it may be necessary to protect certain reactive substituents from unwanted reactions by protection before the sequence described, and to deprotect the substituents afterwards, according to the knowledge of one skilled in the art. Protection and deprotection of functional groups are described, for example, in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999. Reactive substituents which may be protected are shown in Examples 27-33 as, for example, [OH], [SH], *etc.*

Example 27

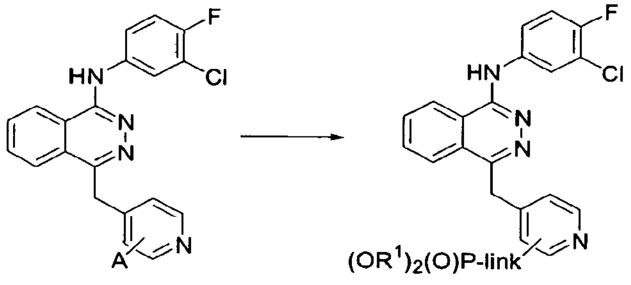
Preparation of Representative Compounds of Formulae 12-13



Illustrated above is the preparation of compounds **27.1** in which A is Br, I, [SH], [NH], *etc.*, or the group link-P(O)(OR^1)$_2$. The preparation of these compounds follows procedures described in J. Med. Chem., 43(12):2310 (2000). The phthalic anhydride **27.8** is melted with a methyl pyridine **27.9** in which A is Br, I, [SH], [NH], *etc.*, or the group link-P(O)(OR^1)$_2$, under high temperature to give **27.3** (the synthesis of **27.9** is described below). The product **27.3** on treatment with hydrazine in water and optionally ethanol, then rearranges to afford the pyridinone **27.4**. Pyridinone **27.4** is then converted to the chloride **27.5** by treatment with a phosphorous oxychloride in an inert solvent such as acetontrile at ca 50°C. The amine, **27.7**, is introduced by heating the chloride **27.5** in the presence of the amine, optionally in a high boiling solvent such as xylenes or DMF to give the amine **27.6**.

Alternatively the pyridinone **27.4** can be directly converted to the product **27.6** in a one step procedure involving melting the aniline, **27.7**, with the pyridinone in the presence of a dehydrating agent such as phosphorus pentoxide as described in J. Med Chem., 43(12):2310 (2000).

The reactions shown above illustrate the preparation of the compounds **27.6** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br, *etc.* Depicted below is the conversion of the compounds **27.6** in which A is [OH], [SH], [NH], Br, *etc.*, into the phosphonate esters **27.1**.

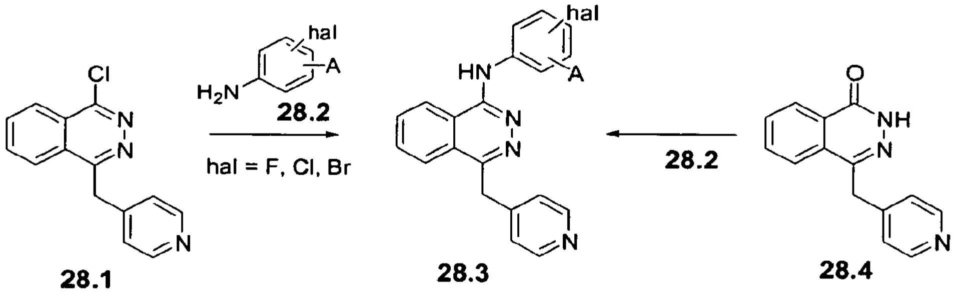


27.6 **27.1**

In this procedure, the compounds **27.6** are converted, using the procedures described herein into the compounds **27.1**.

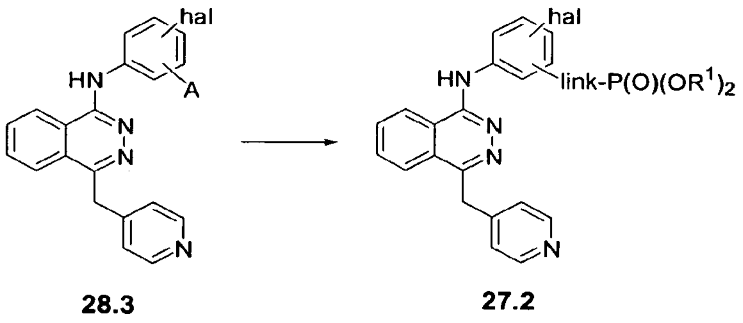
Example 28

Preparation of Representative Compounds of Formulae 12-13



Illustrated above is the preparation of compounds **27.2** in which A is Br, I, [SH], [NH], *etc.*, or the group link-P(O)(OR^1)$_2$. The chloride **28.1**, described in J. Med. Chem., 43(12):2310 (2000), is treated with an aniline **28.2,** in which A is Br, I, [SH], [NH], *etc.* or the group link-P(O)(OR^1)$_2$, as described in Example 27, to give amine **28.3**. Alternatively the pyridinone **28.4**, described in J. Med. Chem., 43(12):2310 (2000) is treated with an aniline **28.2** in which A is Br, I, [SH], [NH], *etc.*, or the group link-P(O)(OR^1)$_2$ as described in Example 27 to give amine **28.3.**

The reactions shown above illustrate the preparation of the compounds **28.3** in which the substituent A is either the group link-P(O)(OR^1)$_2$ or a precursor such as [OH], [SH], [NH], Br, *etc.* Depicted below is the conversion of the compounds **28.3** in which A is [OH], [SH], [NH], Br, *etc.*, into the phosphonate esters **27.2**. In this procedure, the compounds **28.3** are converted, using the procedures described below into the compounds **27.2**.



Examples 29-31

Generally, for Examples 29-31, the reagents used in the synthesis of representative compounds of the invention is as follows:

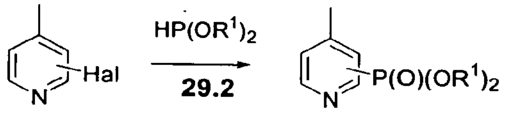
General applicability of methods for introduction of phosphonate substituents

The procedures described for the introduction of phosphonate moieties (Examples 29-33) are, with appropriate modifications known to one skilled in the art, transferable to different chemical substrates. Thus, the methods described above for the introduction of phosphonate groups onto the pyridyl ring of **27.9** are applicable to the introduction of phosphonate moieties onto the aniline **28.2** and the reverse is also true.

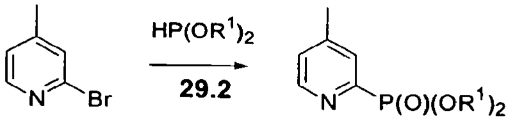
Described generally in Examples 29-31 is the preparation of phosphonate-containing derivatives **27.9**, in which A is Br, Cl, [OH], [NH], and the group link-$P(O)(OR^1)_2$ that are employed in the preparation of the phosphonate ester intermediates **27.1.**

Example 29

Preparation of Representative Compounds of Formulae 12-13



29.1 **29.3**



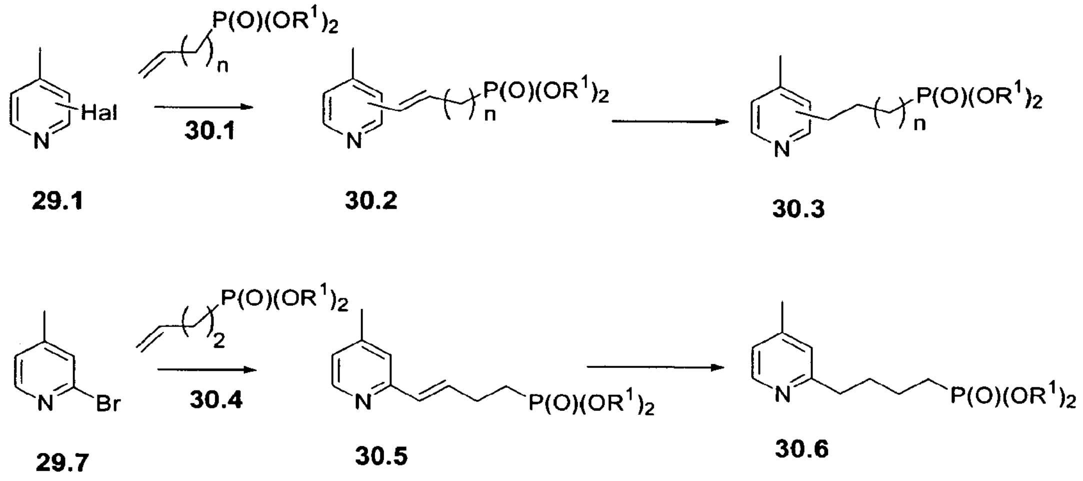
29.4 **29.5**

Described above is the preparation of **27.9** in which the phosphonate is attached directly to the ring. The halo pyridine **29.1** is treated with a dialkyl phosphite **29.2** to give the phosphonate **29.3**. The coupling reaction is conducted in the presence of a palladium (0) catalyst, for example as described in J. Med. Chem., 35:1371 (1992). For example, 2-bromo-4-methyl pyridine

(Aldrich) **29.4** is reacted with an equimolar amount of a dialkyl sodium phosphite **29.2**, in the presence of tetrakis(triphenylphosphine)palladium(0) and triethylamine, in toluene at reflux, to yield the phosphonate **29.5**. Using the above procedures, but employing, in place of the halo pyridine bis(chloromethyl) compound **29.4**, different pyridines **29.1**, and/or different dialkyl sodium phosphites **29.2** the corresponding products **29.3** are obtained.

Example 30

Preparation of Representative Compounds of Formulae 12-13



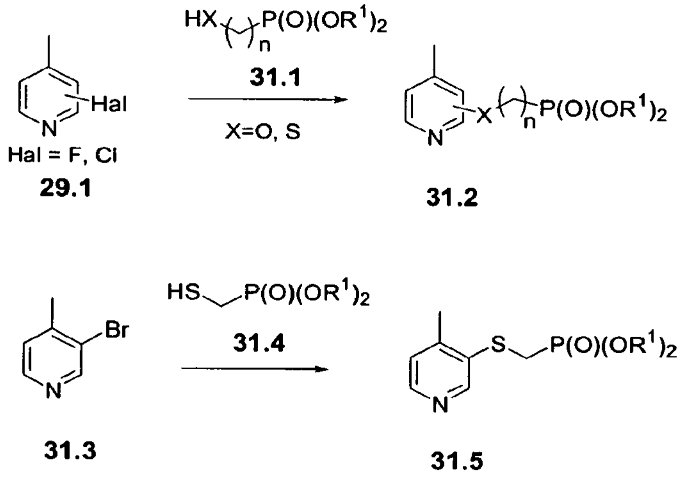
Illustrated above is the preparation of **27.9** in which the phosphonate is attached through a unsaturated or saturated carbon linker. In this procedure, a halo-substituted pyridine **29.1** is coupled, by means of a palladium-catalyzed Heck reaction with a dialkyl alkenyl phosphonate **30.1**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in "Advanced Organic Chemistry," by F. A. Carey and R. J. Sundberg, Plenum, 2001, p. 503ff and in Acc. Chem. Res., 12:146 (1979). The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxane, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate, to afford the coupled product **30.2**.

Optionally, the product **30.2** can be reduced to afford the saturated phosphonate **30.3**. Methods for the reduction of carbon-carbon double bonds are described, for example, in "Comprehensive Organic Transformations," by R. C. Larock, VCH, 1989, p. 6. The methods include catalytic reduction and chemical reduction, the latter, for example, employing diborane or diimide.

For example, as shown above, 2-bromo-4-methyl pyridine **29.4** is reacted with a dialkyl butenyl phosphonate **30.4**, the preparation of which is described in J. Med. Chem., 39:949 (1996) in the presence of bis(triphenylphosphine) palladium(II) chloride as described in J. Med. Chem., 35:1371 (1992), to afford the coupled product **30.5**. Optionally, the product **30.5** is reduced, for example, by reaction with diimide as described in J. Org. Chem., 30:3965 (1965), to afford the saturated product **30.6**. Using the above procedures, but employing, in place of the halo pyridine compound **29.4**, different pyridines **29.1**, and/or different phosphonates **30.1** the corresponding products **30.2** and **30.3** are obtained.

Example 31

Preparation of Representative Compounds of Formulae 12-13



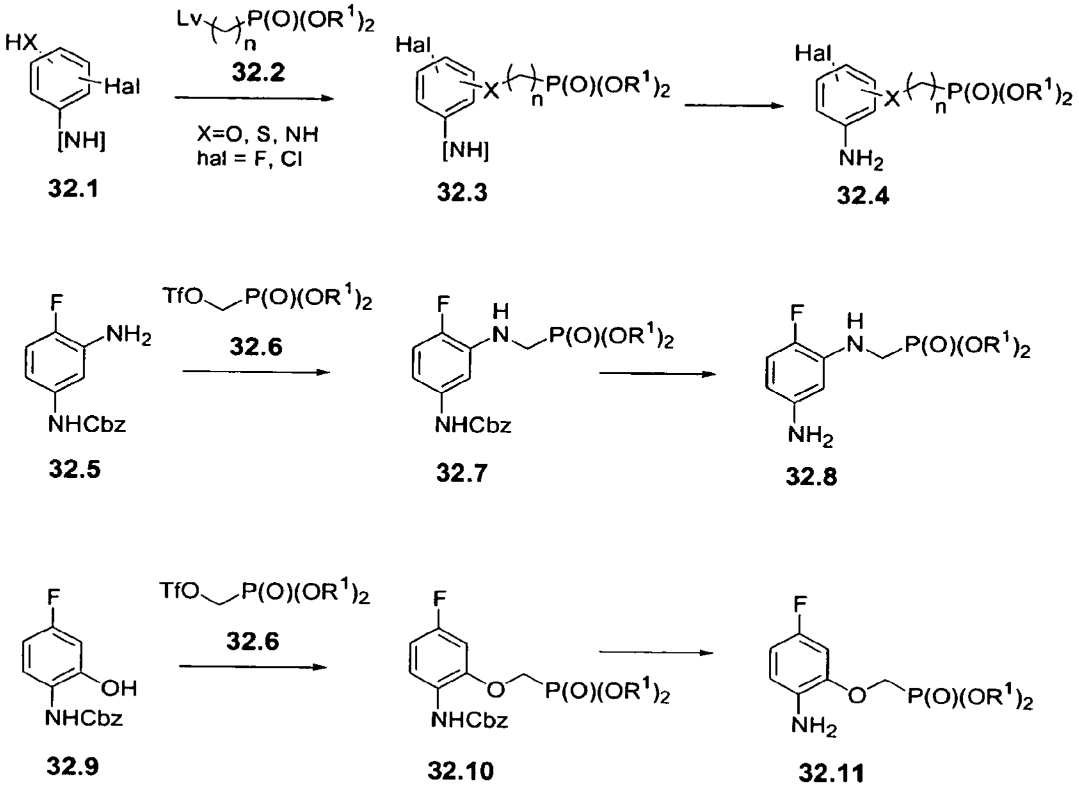
Illustrated above is the preparation of **27.9** in which the phosphonate is attached through a heteroatom, *e.g.*, O, S or N, and a carbon chain. In this procedure, a halo-substituted pyridine **29.1** is reacted with a dialkyl hydroxy- or thio-alkylphosphonate **31.1**. The preparation of alkoxypyridines by the reaction of alkoxides with halopyridines is described, for example, in J. Am. Chem. Soc., 82:4414 (1960). The preparation of pyridine thioethers by reaction of halopyridines with thiols is described, for example, in "Chemistry of Heterocyclic Compounds, Pyridine and its Derivatives," E. Klingsberg, Ed, part 4, p. 358. The alcohols and thiols are transformed into metal salts, for example sodium or potassium salts, and then reacted with the halopyridine substrates at elevated temperatures, optionally in the presence of copper powder catalyst, to afford the ether or thioether products **31.2**. For example, a tetrahydrofuran solution of 3-bromo-4-methylpyridine **31.3** (Aldrich) is heated at reflux with an equimolar amount of a dialkyl 2-mercaptoethylphophonate **31.4**, the preparation of which is described in Aust. J. Chem., 43:1123 (1990), in the presence of sodium carbonate, to afford the thioether product **31.5**.

Using the above procedures, but employing, in place of the halopyridines **31.3**, different halopyridines **29.1**, and/or different hydroxy or thio-alkyl phosphonates **31.1**, the corresponding products **31.2** are obtained.

Examples 32-33

Described generally in Examples 32-33 is the preparation of phosphonate-containing derivatives **28.3**, in which A is Br, Cl, [OH], [NH], and the group link-P(O)(OR^1)$_2$ that are employed in the preparation of the phosphonate ester intermediates **27.2**.

Example 32

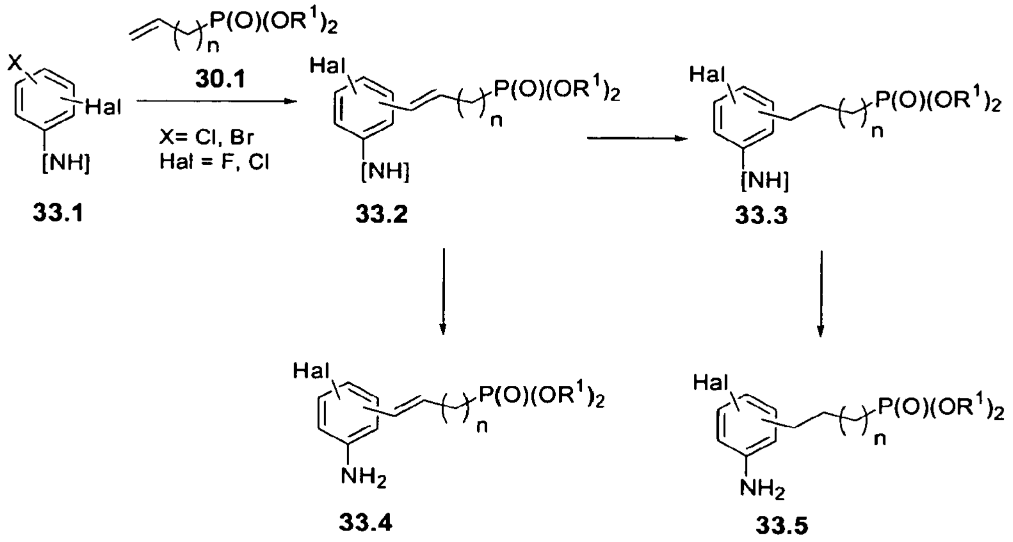

HX
Hal
[NH]
32.1
Lv P(O)(OR^1)$_2$
n
32.2
X=O, S, NH
hal = F, Cl
Hal
X
n
P(O)(OR^1)$_2$
[NH]
32.3
Hal
X
n
P(O)(OR^1)$_2$
NH$_2$
32.4
F
NH$_2$
NHCbz
32.5
TfO P(O)(OR^1)$_2$
32.6
F
H
N P(O)(OR^1)$_2$
NHCbz
32.7
F
H
N P(O)(OR^1)$_2$
NH$_2$
32.8
F
OH
NHCbz
32.9
TfO P(O)(OR^1)$_2$
32.6
F
O P(O)(OR^1)$_2$
NHCbz
32.10
F
O P(O)(OR^1)$_2$
NH$_2$
32.11

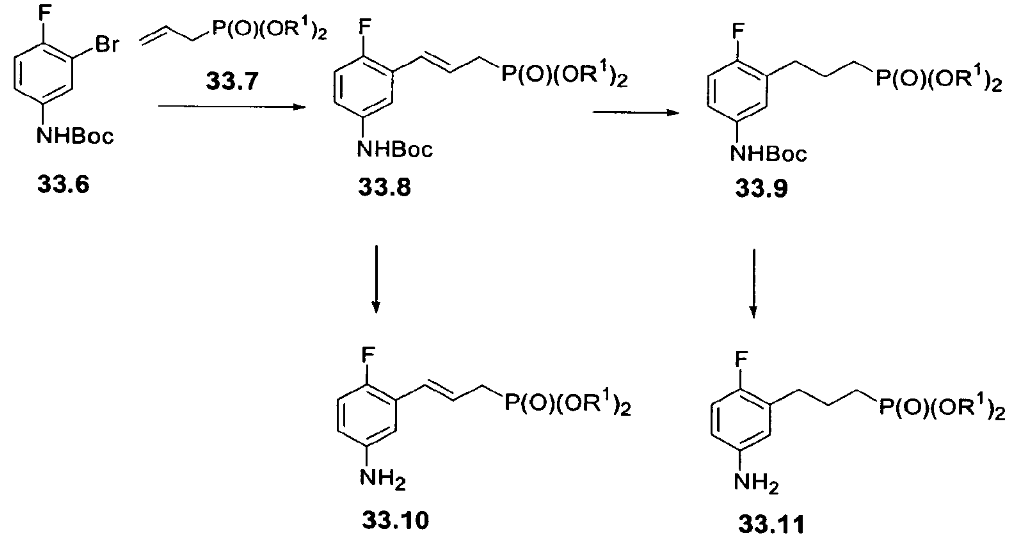
Illustrated above is the preparation of **28.2** (see Example 28) in which the phosphonate is attached through a heteroatom, *e.g.*, O, S, or N, and a carbon linker. In this procedure, an optionally protected aniline is reacted with an alkylphosphonate **32.2** in which Lv is a leaving group such as triflate, Br, Cl, Mesyl, *etc.*, in the presence of a suitable base. The base required for this transformation depends on the nature of the heteroatom X. For example, if X is N or S, an excess of an inorganic base such as, for example, potassium carbonate, in the presence of an organic solvent such as dimethylformamide, is suitable. The reaction proceeds at from ambient temperature to about 80° to afford the displacement products **32.3**. If X is O, an equimolar amount of a strong base, such as, for example, lithium hexamethyldisilylazide and the like, is employed, in the presence of a solvent such as tetrahydrofuran. Deprotection, of the amine group as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 ch 7. then affords the amine **32.4**.

For example, the diamine **32.5** (Aldrich), mono-protected as the CBZ carbamate as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 p531ff, is treated with an equimolar amount of triflate **32.6**, the preparation of which is described in Tet. Lett., 27:1497 (1986), in dimethylformamide containing excess potassium carbonate, at ca 60° to afford the phosphonate product **32.7**. Deprotection by reduction over palladium on carbon in the presence of hydrogen then affords the amine **32.8.** Using the above procedures, but employing, in place of the aniline **32.5**, different anilines **32.1**, and/or different alkylphosphonates **32.2**, the corresponding products **32.4** are obtained.

Alternatively , the aminophenol **32.9**, protected as the CBZ carbamate as described above, is reacted with one equivalent of an alkylphosphonate **32.6**, as described above, to give phosphonate **32.10.** Removal of the CBZ group by catalytic reduction over palladium on carbon in the presence of hydrogen then affords the amine **32.11.**

Example 33


P(O)(OR^1)$_2$
n
30.1
X= Cl, Br
Hal = F, Cl
X
Hal
[NH]
33.1
33.2
33.3
33.4
33.5
NH$_2$


F
Br
NHBoc
P(O)(OR^1)$_2$
33.6
33.7
33.8
33.9
33.10
33.11
NH$_2$

Illustrated above is the preparation of **28.2** (see Example 28) in which the phosphonate is attached through a unsaturated or saturated carbon linker. In this procedure, an optionally protected halo-substituted aniline **33.1** is coupled, by means of a palladium-catalyzed Heck reaction with a dialkyl alkenyl phosphonate **30.1**, as described in Example 30, to afford the coupled product **33.2**. Protection of anilines is described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 ch 7. Preferably the aniline is treated with a BOC reagent such as BOC chloride, or BOC anhydride in the presence of DMAP and a base, *e.g.*, triethylamine to afford the protected aniline.

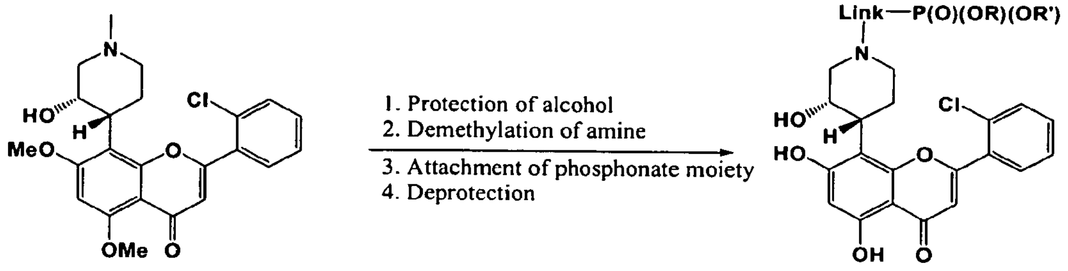
Optionally, the coupled product **33.2** can be reduced, as described in Example 30, to afford the saturated phosphonate **33.3**. Removal of the protecting groups, as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M Wuts, Wiley, Third Edition 1999 ch 7., affords the anilines **33.4** and **33.5**.

For example, BOC protected 3-bromo-4-fluoro aniline **33.6** (Aldrich) is reacted with a dialkyl propenyl phosphonate **33.7**, the preparation of which is described in J. Med. Chem., 39:949 (1996), in the presence of bis(triphenylphosphine) palladium(II) chloride , as described in J. Med. Chem., 35:1371 (1992), to afford the coupled product **33.8**. The BOC protection of the aniline is performed by treating the aniline with BOC anhydride in the presence of DMAP. The product **33.8** is reduced, for example by reaction with diimide, as described in J. Org. Chem., 30:3965 (1965), to afford the saturated product **33.9**. Treatment of **33.8** and **33.9** with TFA in THF or dioxane, then affords the products **33.10** and **33.11**, respectively. Using the above procedures, but employing, in place of the halo pyridine compound **33.6**, different pyridines **33.1**, and/or different phosphonates **30.1** the corresponding products **33.4** and **33.5** are obtained.

Example 34

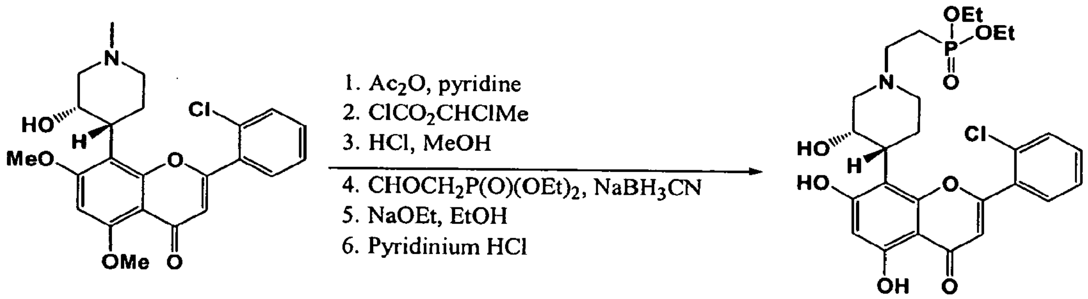
Preparation of Representative Compounds of Formulae 14-15

Representative compounds of the invention can be prepared according to the following methods.


Link—P(O)(OR)(OR')
1. Protection of alcohol
2. Demethylation of amine
3. Attachment of phosphonate moiety
4. Deprotection
HO
H
MeO
Cl
O
OMe
N
OH

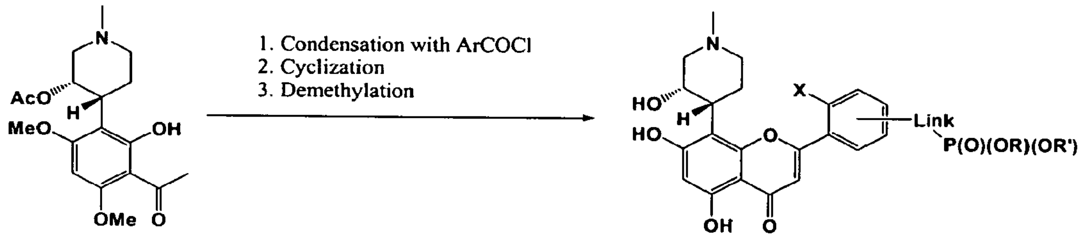
The bis-anisole derivative of flavopiridol (see Bioorg. Med. Chem. Lett., 10:1037 (2000)) serves as an ideal starting point for attachment of a phosphonate moiety to the piperidine nitrogen. Following protection of the alcohol, the tertiary amine is demethylated and derivatized with the reagent of choice. Removal of the methyl ethers and the protecting group on the alcohol gives the desired analogs.

The synthesis of a specific compound of the invention, an alvocidib analog with a phosphonate moiety linked to the piperidine nitrogen, is illustrated below.


1. Ac$_2$O, pyridine
2. ClCO$_2$CHClMe
3. HCl, MeOH
4. CHOCH$_2$P(O)(OEt)$_2$, NaBH$_3$CN
5. NaOEt, EtOH
6. Pyridinium HCl
OEt
OEt
P
O
N
HO
H
MeO
Cl
OMe
OH

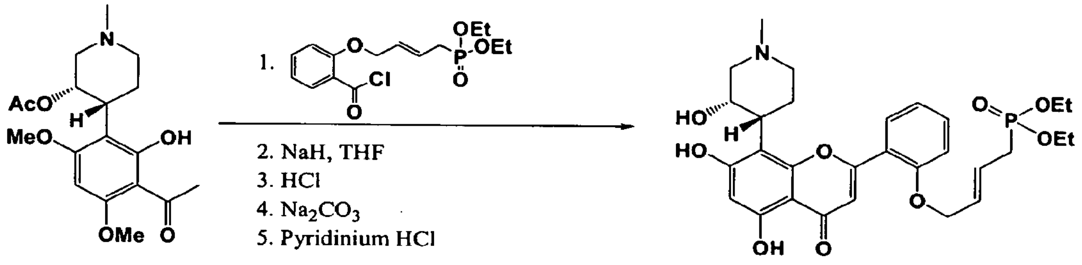
The alcohol is protected as the acetate under standard conditions (see Greene, T., "Protective groups in Organic Synthesis," Wiley-Interscience, 1999). Demethylation of the N-methylpiperidine is achieved through reaction with α-chloroethyl chloroformate in the presence of a base such as *N,N*-

diisopropylethylamine (DIEA) followed by brief heating in acidic methanol. The liberated secondary amine is condensed with (2-oxo-ethyl)-phosphonic acid diethyl ester under reductive conditions such as those achieved through the use of sodium cyanoborohydride in a solvent such as methanol or dimethylformamide (see Tet. Lett., 31:5595 (1990)). The alcohol is de-acetylated by treatment with sodium ethoxide in ethanol. Finally, bis-demethylation is achieved by heating with pyridinium hydrochloride (see Bioorg. Med. Chem. Lett., 10:1037 (2000)).



AcO
H
MeO
OH
OMe
O
1. Condensation with ArCOCl
2. Cyclization
3. Demethylation
HO
H
HO
O
X
Link
P(O)(OR)(OR')
OH
O

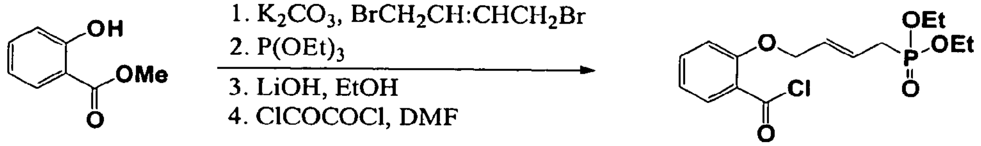
The 2-hydroxyacetophenone (see Bioorg. Med. Chem. Lett., 10:1037 (2000)) is treated with a suitable phosphonate-bearing benzoyl chloride derivative. The flavone ring system is formed by cyclization, and the methyl groups are removed. Such a synthesis is exemplified below.



AcO
H
MeO
OH
OMe
O
1.
O
OEt
P
OEt
O
Cl
O
2. NaH, THF
3. HCl
4. Na2CO3
5. Pyridinium HCl
HO
H
HO
O
O
P
OEt
OEt
O
OH
O

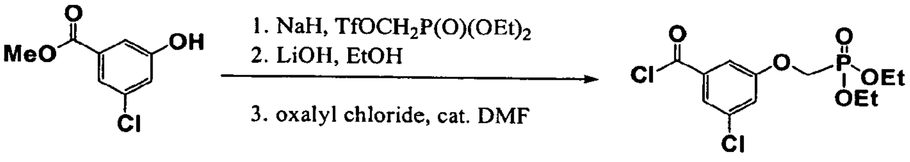
Condensation with [4-(2-chlorocarbonyl-phenoxy)-but-2-enyl]-phosphonic acid diethyl ester (synthesis below) is followed by successive treatment with sodium hydride, hydrochloric acid and sodium carbonate, generating the 5,7-dimethoxyflavone. Demethylation to provide the 5,7-dihydroxyflavone final product is achieved as above (see also Bioorg. Med. Chem. Lett., 10:1037 (2000)).

The synthesis of another specific compound of the invention [4-(2-chlorocarbonyl-phenoxy)-but-2-enyl]-phosphonic acid diethyl ester, is illustrated below.


OH
OMe
O
1. K₂CO₃, BrCH₂CH:CHCH₂Br
2. P(OEt)₃
3. LiOH, EtOH
4. ClCOCOCl, DMF
O
Cl
O
OEt
P
OEt
O

Salicylic acid methyl ester is treated in a solvent such as dimethylformamide or tetrahydrofuran with a base such as sodium hydride. When bubbling ceases, *E*-1,4-dibromobutene is added in excess. After quenching the reaction with aqueous ammonium chloride and extracting the product with an organic solvent such as ethyl acetate, the mono-alkylated product is isolated by chromatography. The resulting monobromide is heated with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction conditions: see Engel, R., "Synthesis of Carbon-phosphorus Bonds," CRC press, 1988) to generate the diethyl ester of the desired phosphonic acid. The methyl ester is saponified with lithium hydroxide and the acid chloride generated by treatment with oxalyl chloride in a solvent such as dichloromethane in the presence of a catalytic amount of dimethylformamide.

Syntheses of another specific compound of the invention is shown below.


O
MeO
OH
Cl
1. NaH, TfOCH₂P(O)(OEt)₂
2. LiOH, EtOH
3. oxalyl chloride, cat. DMF
O
Cl
O
Cl
O
P
OEt
OEt

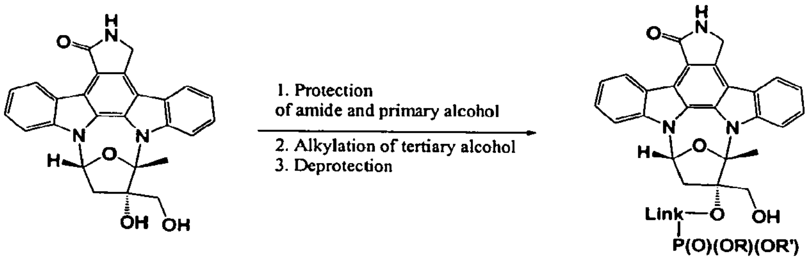
The phenol is treated in a solvent such as tetrahydrofuran or dimethylformamide with a base such as sodium hydride. When bubbling ceases, diethyl phosphonomethyltriflate (prepared according to Tetrahedron Lett., 27:1477 (1986)) is added, yielding the desired phosphonate diester.

Similarly, a reagent suitable for generating an analog with a phosphonate moiety attached to the 4-position of the phenyl ring at the flavone 2-position may be generated from 4-hydroxybenzoic acid methyl ester.

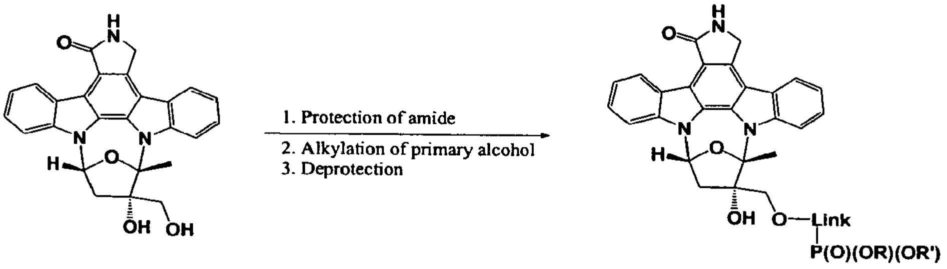
Example 35

Preparation of Representative Compounds of Formulae 16-18

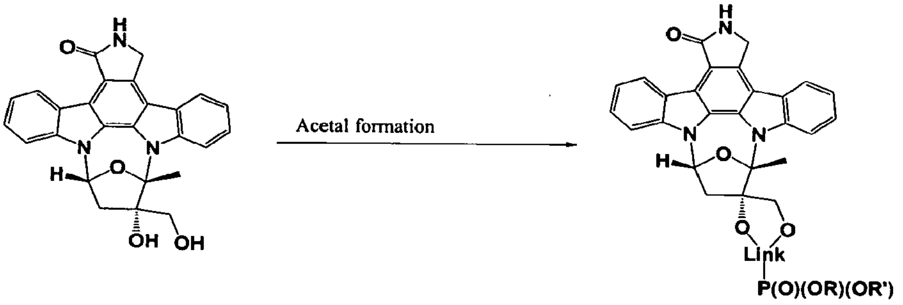
In general, representative compounds of the invention can be prepared as follows:



1. Protection of amide and primary alcohol
2. Alkylation of tertiary alcohol
3. Deprotection
Link—O
P(O)(OR)(OR')

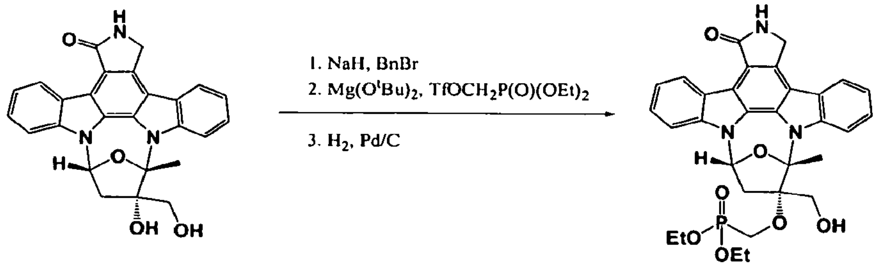


1. Protection of amide
2. Alkylation of primary alcohol
3. Deprotection
O—Link
P(O)(OR)(OR')



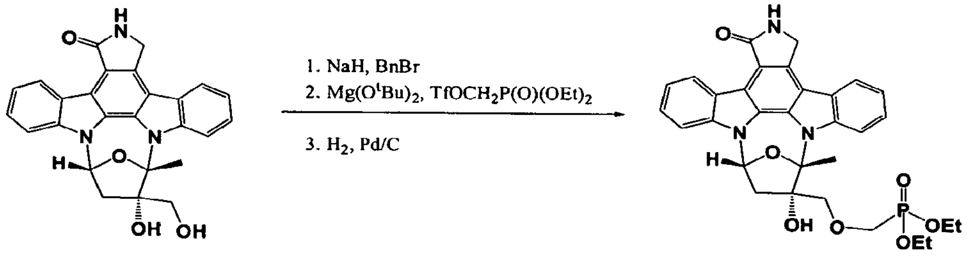
Acetal formation
Link
P(O)(OR)(OR')

The preparation of a specific compound of the invention is shown below:



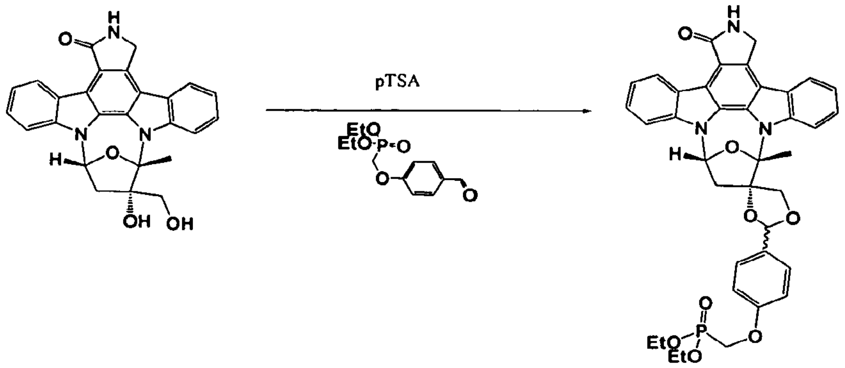
CEP-701 can be treated in a solvent such as dimethylformamide or tetrahydrofuran with two equivalents of a base such as sodium hydride. When bubbling ceases, benzyl bromide is added in excess, yielding the doubly-protected intermediate. After further treatment with a base such as magnesium *tert*-butoxide, diethyl phosphonomethyltriflate (prepared according to Tetrahedron Lett., 27:1477 (1986)) is added, yielding the desired phosphonate diester. Final deprotection by hydrogenation over a catalyst such as palladium on charcoal in a solvent such as methanol as described in Greene, T., "Protective Groups in Organic Synthesis," Wiley-Interscience, 1999, provides the desired product.

Another specific compound of the invention can be prepared as follows:



CEP-701 can be treated in a solvent such as dimethylformamide or tetrahydrofuran with one equivalent of a base such as sodium hydride or cesium carbonate. Benzyl bromide is added, yielding the N-benzylated product. After further treatment with a base such as magnesium *tert*-butoxide, diethyl phosphonomethyltriflate is added, yielding the desired phosphonate diester. Final deprotection by hydrogenation over a catalyst such as palladium on charcoal in a solvent such as methanol utilizing the method described in Greene (see above) provides the desired product.

Another specific compound of the invention can be synthesized as follows:

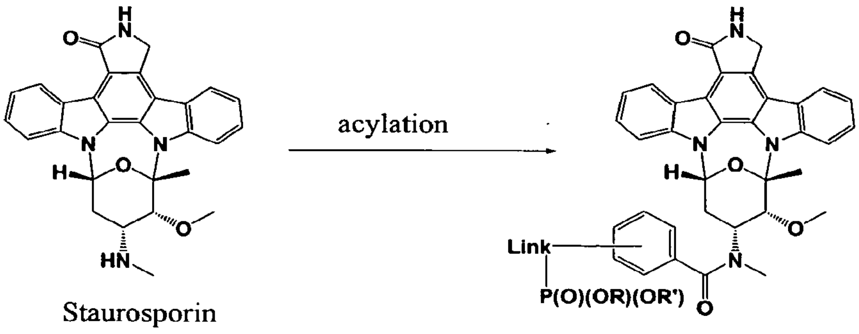


(4-Formyl-phenoxymethyl)-phosphonic acid diethyl ester is generated by treatment of 4-hydroxybenzaldehyde, in a solvent such as dimethylformamide or tetrahydrofuran, with a base such as sodium hydride and diethyl phosphonomethyltriflate. The product is condensed with CEP-701 in a solvent such as toluene, in the presence of a catalytic amount of *p*-toluenesulfonic acid, with azeotropic removal of the water so formed, yielding the desired acetal.

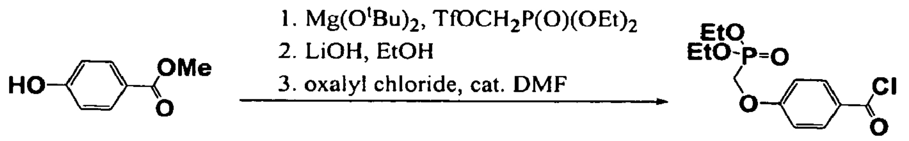
Example 36

Preparation of Representative Compounds of Formulae 19-21

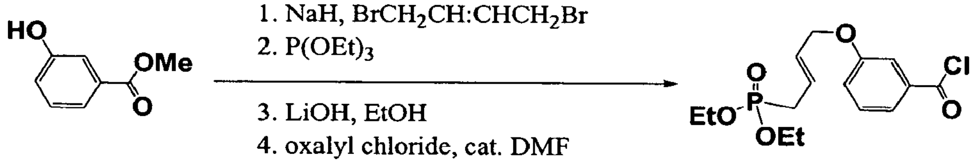
Representative compounds of the invention can be made according to the following:



Staurosporin is acylated with activated benzoic acid derivatives such as benzoyl chlorides in a solvent such as chloroform, in the presence of a base such as *N,N*-diisopropylethylamine (DIEA) (Bioorg. Med. Chem. Lett., 4:399 (1994)). Specifically, examples of benzoyl chlorides for use in the synthesis of suitable phosphonate-containing midostaurin analogs are illustrated below.

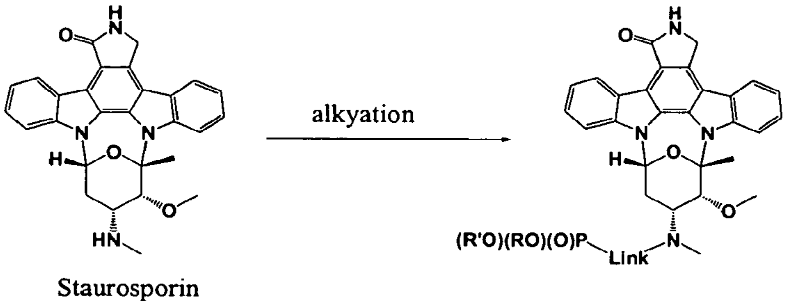

1. $Mg(O^tBu)_2$, $TfOCH_2P(O)(OEt)_2$
2. LiOH, EtOH
3. oxalyl chloride, cat. DMF

4-Hydroxybenzoic acid methyl ester is treated with magnesium tert-butoxide and diethyl phosphonomethyltriflate (prepared according to Tetrahedron Lett., 27:1477 (1986)) in a solvent such as tetrahydrofuran. The resulting 4-(diethoxyphosphorylmethoxy)benzoic acid methyl ester is saponified with lithium hydroxide in ethanol, and the acid chloride is generated from the benzoic acid by reaction with oxalyl chloride in a solvent such as dichloromethane, catalyzed by dimethylformamide.

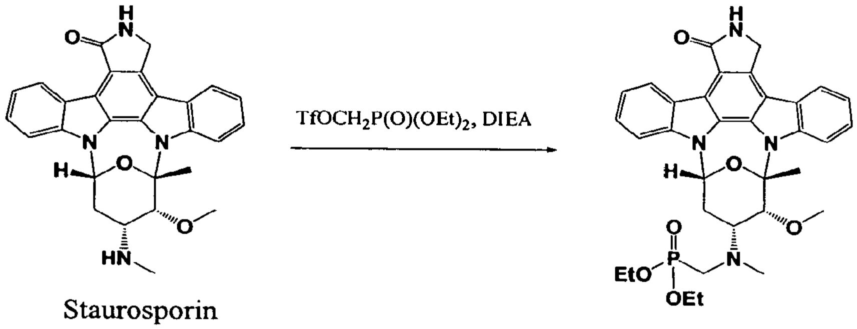


3-Hydroxybenzoic acid methyl ester is treated in a solvent such as dimethylformamide or tetrahydrofuran with a base such as sodium hydride. When bubbling ceases, *E*-1,4-dibromobutene is added in excess. After quenching the reaction with aqueous ammonium chloride and extracting the product with an organic solvent such as ethyl acetate, the mono-alkylated product is isolated by chromatography. The bromide is heated with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction conditions: see Engel, R., "Synthesis of Carbon-phosphorus Bonds," CRC press, 1988) to generate 3-[4-(diethoxy-phosphoryl)-but-2-enyloxy]-benzoic acid methyl ester. The remaining steps are similar to those described above.

In addition, representative compounds of the invention can be prepared as follows:


alkyation
Staurosporin
(R'O)(RO)(O)P
Link

Alkylations on the secondary amine of staurosporine have been carried out under a variety of standard conditions: see Bioorg. Med. Chem. Lett., 4:399 (1994). An example of the synthesis of a phosphonate-containing alkyl derivative, which is another specific compound of the invention, is shown below:

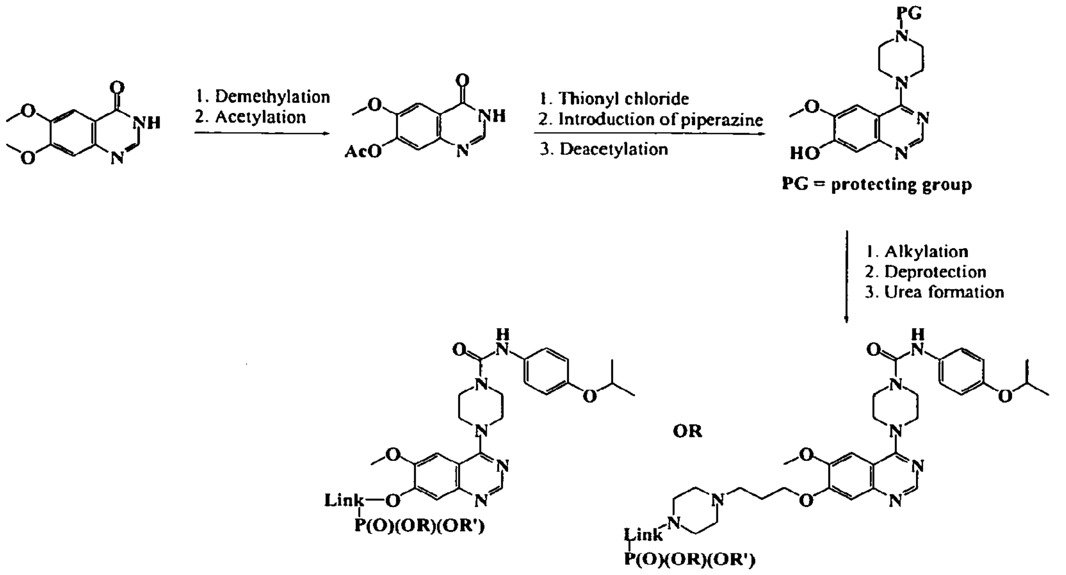

$TfOCH_2P(O)(OEt)_2$, DIEA
Staurosporin
EtO
OEt

Staurosporin is alkylated with diethyl phosphonomethyltriflate in the presence of a base such as DIEA.

Example 37

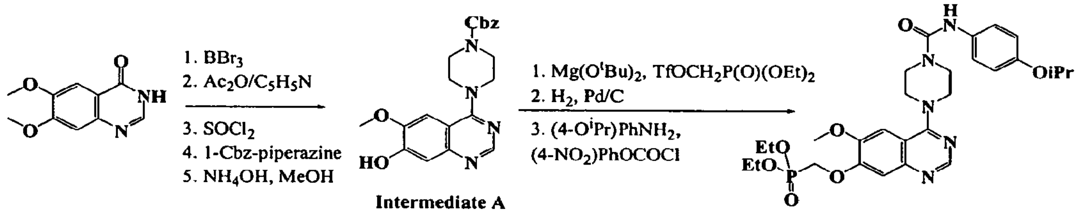
Preparation of Representative Compounds of Formulae 22-24

Representative compounds of the invention can be prepared as generally described below.


1. Demethylation
2. Acetylation
1. Thionyl chloride
2. Introduction of piperazine
3. Deacetylation
PG = protecting group
1. Alkylation
2. Deprotection
3. Urea formation
OR
Link—O
P(O)(OR)(OR')
Link
P(O)(OR)(OR')

Introduction of the phosphonate-bearing entity at the quinazoline 7-position is most conveniently achieved by alkylation of a suitably-protected 4-piperazinylquinazoline, prior to urea formation.

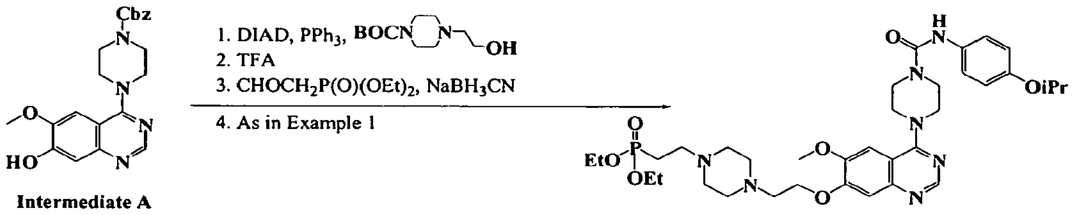
A specific compound of the invention can be prepared as follows:


1. BBr3
2. Ac2O/C5H5N
3. SOCl2
4. 1-Cbz-piperazine
5. NH4OH, MeOH
Intermediate A
1. Mg(OtBu)2, TfOCH2P(O)(OEt)2
2. H2, Pd/C
3. (4-OiPr)PhNH2, (4-NO2)PhOCOCl
OiPr

6,7-Dimethoxy-3,4-dihydroquinazolin-4-one is reacted with boron tribromide to give a mixture of mono-demethylated products. Although these may be separated by chromatography at this stage, the separation may be more conveniently achieved on the mixture of acetates that arises from reaction with and acetylating reagent such as acetyl chloride in the presence of a base such as pyridine. The desired isomer is reacted with thionyl chloride (see Bioorg. Med. Chem. Lett., 11:1911 (2001)) and the resulting 4-chloroquinazoline is treated with piperazine-1-carboxylic acid benzyl ester. The acetyl protecting group is removed under standard conditions such as by treatment with ammonia in methanol (see Greene, T., "Protective Groups in Organic Synthesis," Wiley-Interscience, 1999) to generate Intermediate A.

Upon treatment with a base such as magnesium *tert*-butoxide and diethyl phosphonomethyltriflate (prepared according to Tetrahedron Lett., 27:1477 (1986)), the phosphonate-bearing moiety is introduced at the quinazoline 7-position. Thereafter, removal of the benzyl carbamate protecting group by hydrogenation over a catalyst such as palladium on charcoal in a solvent such as methanol (see Greene, *ibid*) and condensation with 4-isopropoxyaniline (commercially available) and 4-nitrophenyl chloroformate provides the desired compound.

Another specific compound of the invention is prepared as follows:

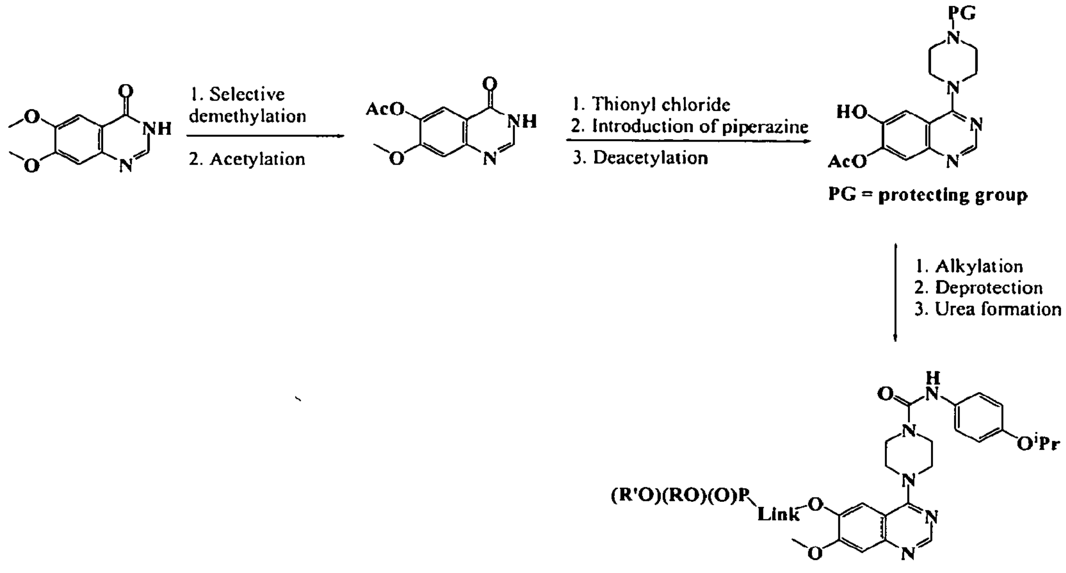


Intermediate A may be alkylated on the phenol by reaction with 4-(2-hydroxy-ethyl)-piperazine-1-carboxylic acid tert-butyl ester in the presence of an azodicarboxylate diester such as diisopropyl azodicarboxylate and triphenylphosphine, as described by Mitsunobu (Bull. Chem. Soc. Japan., 44:3427 (1971)). Following deprotection with trifluoroacetic acid, the liberated secondary amine is condensed with (2-oxo-ethyl)-phosphonic acid diethyl ester under reductive conditions such as those achieved through the use of sodium cyanoborohydride in a solvent such as methanol or dimethylformamide (see Tet. Lett., 31:5595 (1990)). The remaining steps are similar to those described above.

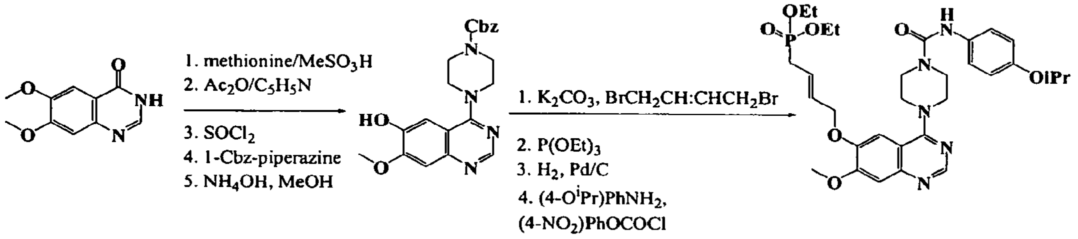
Example 38

Preparation of Representative Compounds of Formulae 22=24

Representative compounds of the invention can be prepared as follows:


1. Selective demethylation
2. Acetylation
AcO
1. Thionyl chloride
2. Introduction of piperazine
3. Deacetylation
HO
AcO
PG
PG = protecting group
1. Alkylation
2. Deprotection
3. Urea formation
(R'O)(RO)(O)P
Link
OⁱPr

The route is similar to that shown in Example 37, but exploits a selective demethylation at the 6-position of 6,7-dimethoxy-3,4-dihydroquinazolin-4-one (see Bioorg. Med. Chem. Lett., 11:1911 (2001)). A specific example of such a synthesis is shown below.

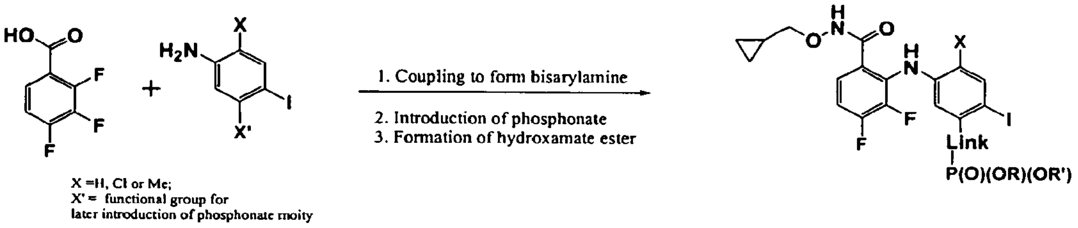

1. methionine/MeSO$_3$H
2. Ac$_2$O/C$_5$H$_5$N
3. SOCl$_2$
4. 1-Cbz-piperazine
5. NH$_4$OH, MeOH
Cbz
HO
1. K$_2$CO$_3$, BrCH$_2$CH:CHCH$_2$Br
2. P(OEt)$_3$
3. H$_2$, Pd/C
4. (4-O^{i}Pr)PhNH$_2$, (4-NO$_2$)PhOCOCl
OEt
OEt
OIPr

Following the selective demethylation, the steps are similar to those discussed in previous examples up to the point where a phenol is alkylated. In this example, however, the alkylation is performed with *E*-1,4-dibromobutene, and the monobromide product is reacted with triethylphosphite in a solvent such as toluene toluene (or other Arbuzov reaction conditions: see Engel, R., "Synthesis of Carbon-phosphorus Bonds," CRC press, 1988) to generate the diethyl ester of the desired phosphonic acid. Thereafter, the steps are again similar to those described in previous examples.

Example 39

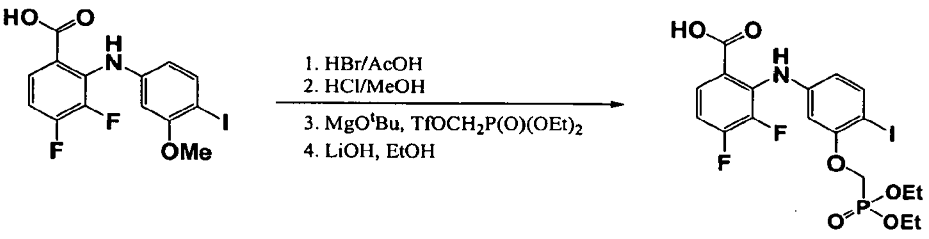
Preparation of Representative Compounds of Formulae 25-26

Compounds of the invention can be prepared as generally described below.


HO
O
F
F
F
H2N
X
I
X'
1. Coupling to form bisarylamine
2. Introduction of phosphonate
3. Formation of hydroxamate ester
X =H, Cl or Me;
X' = functional group for later introduction of phosphonate moity
O
N
H
H
N
X
F
F
I
Link
P(O)(OR)(OR')

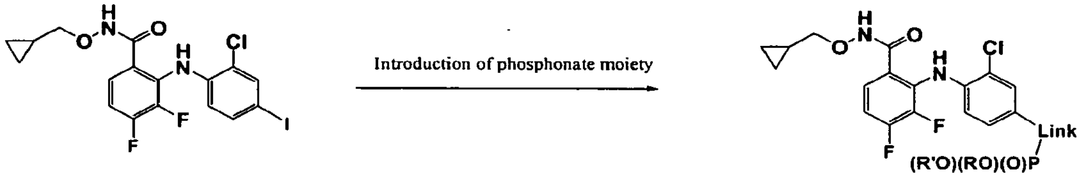
The coupling of an aniline with 2,3,4-trifluorobenzoic acid is performed in the presence of a large excess of a base such as lithium diisopropylamide in a solvent such as tetrahydrofuran, and at temperatures at or below ambient, as described in patent application WO 2001-US22948. The subsequent introduction of a phosphonate moeity may be achieved by a variety of means, such as those illustrated below. Thereafter, the hydroxamic ester is generated by treatment of the benzoic acid with O-(tetrahydro-2H-pyran-2-yl)hydroxylamine and diisopropylethylamine in the presence of a coupling reagent such as benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP) in a solvent such as tetrahydrofuran or dichloromethane, as described in patent application WO 2000-US18347 20000705, followed by treatment with ethanolic hydrochloric acid.

A specific compound of the invention can be synthesized as follows:

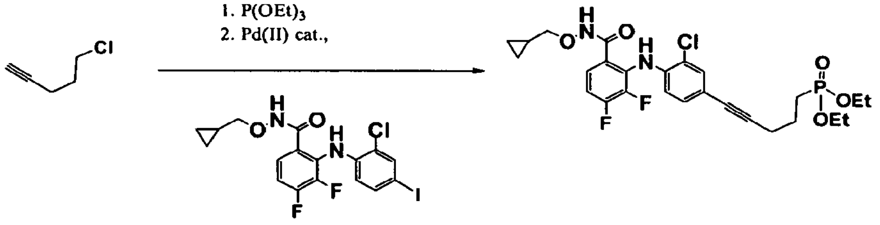

HO
O
H
N
F
F
I
OMe
1. HBr/AcOH
2. HCl/MeOH
3. MgO^{t}Bu, TfOCH$_2$P(O)(OEt)$_2$
4. LiOH, EtOH
HO
O
H
N
F
F
I
O
OEt
O
P
OEt

Having coupled 2,3,4-trifluorobenzoic acid with 2-iodo-5-nitroanisole (commercially available), the methyl ether is removed under standard conditions such as by treatment with hydrobromic acid in acetic acid (see Greene, T., "Protective Groups in Organic Synthesis," Wiley-Interscience, 1999). The benzoic acid is esterified by dissolution in acidic methanol. The phenol is then treated in a solvent such as tetrahydrofuran or dimethylformamide with a base such as sodium hydride. When bubbling ceases, diethyl phosphonomethyltriflate (prepared according to Tetrahedron Lett., 27:1477 (1986)) is added, yielding the desired phosphonate diester. Saponification of the benzoic aicd (ready for coupling to form the hydroxamate ester; see above) is achieved with lithium hydroxide in a solvent such as tetrahydrofuran or ethanol.

In addition, representative compounds of the invention are prepared as follows:



The iodo substituent present in PD-184352 may be used for the introduction of a phosphonate-bearing moiety, as illustrated below.

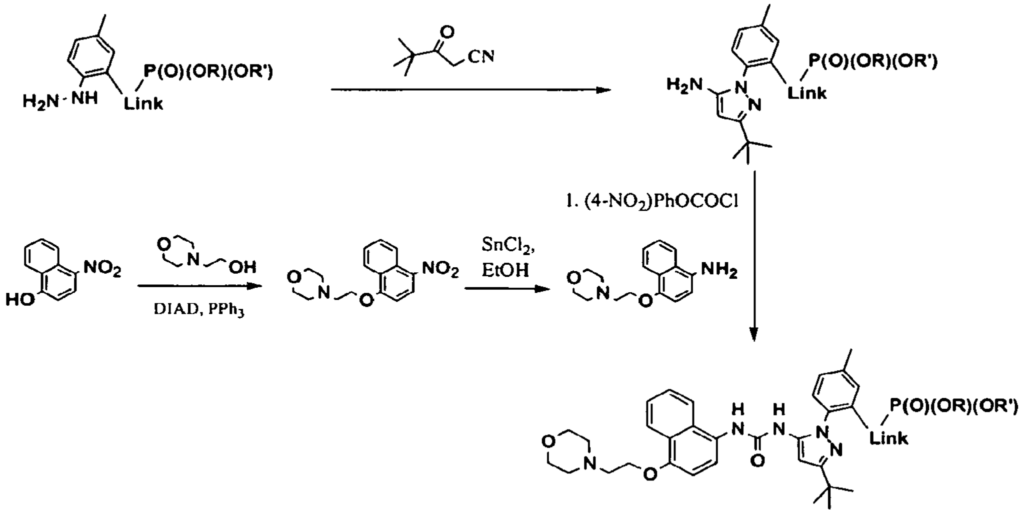


5-Chloro-1-pentyne is treated with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction conditions: see Engel, R., "Synthesis of Carbon-phosphorus Bonds," CRC press, 1988) to generate the diethyl ester of the desired phosphonic acid. This acetylene is coupled with PD-184352 under conditions such as those pioneered by Sonagashira (Sonogashira *et al.*, Tetrahedron Lett., 4467 (1975)).

Example 40

Preparation of Representative Compounds of Formulae 27-30

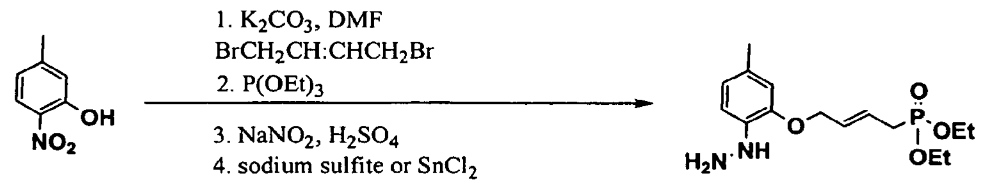
Compounds of the invention can be prepared as generally outlined below.



P(O)(OR)(OR')
Link
H₂N·NH
CN
H₂N
1. (4-NO₂)PhOCOCl
NO₂
HO
OH
DIAD, PPh₃
SnCl₂, EtOH
NH₂

The aryl hydrazine is condensed with 4,4-dimethyl-3-oxo-pentanenitrile to form an aminopyrazole (as described in J. Med. Chem., 45:2994 (2002)). Urea formation is accomplished by sequential condensation with 4-nitrophenyl chloroformate and the requisite aniline. The latter is generated from 4-nitro-naphthalen-1-ol by reaction with 2-morpholin-4-yl-ethanol using a method such as that described by Mitsunobu (Bull. Chem. Soc. Japan, 44:3427 (1971)), followed by tin(II)-mediated reduction of the nitro group to reveal the aniline.

The synthesis of a specific compound of the invention, *e.g.*, suitable phosphonate-containing arylhydrazine, is illustrated below.

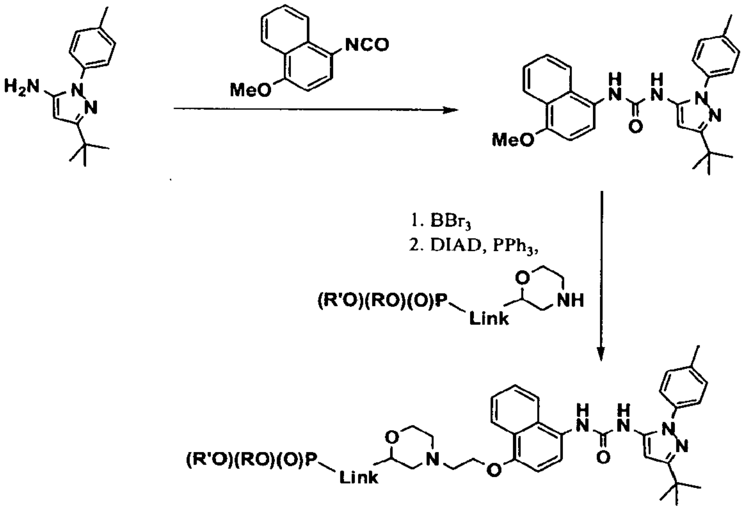


OH
NO₂
1. K₂CO₃, DMF
BrCH₂CH:CHCH₂Br
2. P(OEt)₃
3. NaNO₂, H₂SO₄
4. sodium sulfite or SnCl₂
O
P
OEt
OEt
H₂N·NH

5-Methyl-2-nitrophenol is alkylated with *E*-1,4-dibromobutene. The resulting monobromide is heated with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction conditions: see Engel, R., "Synthesis of Carbon-phosphorus Bonds," CRC press, 1988) to generate the diethyl ester of the desired phosphonic acid. The nitro group is converted to the aryl hydrazine by diazotization and reduction with sodium sulfite (Chem. Ber., 93:540 (1960)) or tin(II) chloride (J. Med. Chem., 44:4031 (2001)).

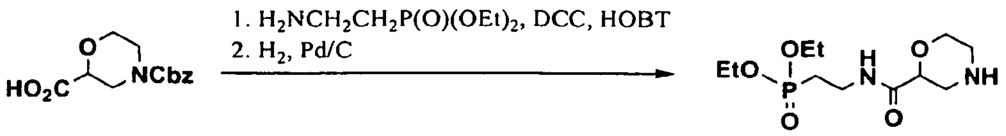
The syntheses of suitable phosphonate-containing aryl hydrazines in which link is attached to the 3- or 4-positions of the phenyl ring are analogous to that shown above, starting from 2-methyl-5-nitrophenol and 4-nitrophenol, respectively.

In addition, representative compounds of the invention can be synthesized as shown below:



Following the synthesis of the urea through condensation of 5-tert-butyl-2-p-tolyl-2H-pyrazol-3-ylamine and 1-isocyanato-4-methoxy-naphthalene, the product is demethylated by treatment with a Lewis acid such as boron tribromide. The resulting phenol is coupled with a suitable morpholine derivative using a method such as that described by Mitsunobu (Bull. Chem. Soc. Japan., 44:3427 (1971)).

The synthesis of a specific compound of the invention, *e.g.*, suitable phosphonate-containing morpholine derivative, is illustrated below.

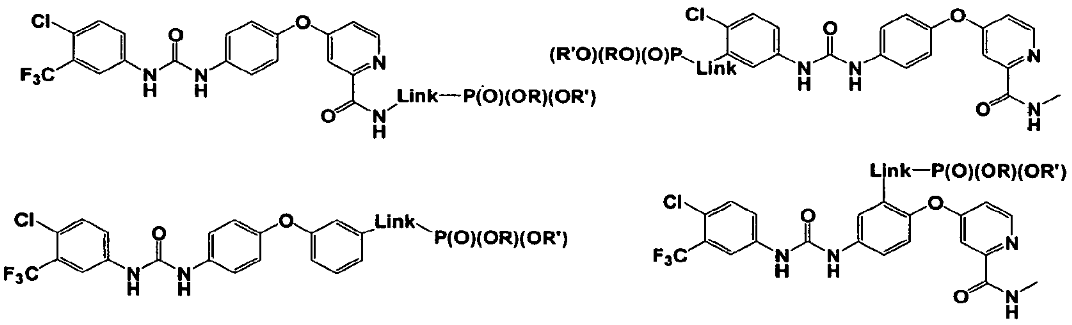

1. H2NCH2CH2P(O)(OEt)2, DCC, HOBT
2. H2, Pd/C
HO2C
NCbz
EtO
OEt
NH

Morpholine-2,4-dicarboxylic acid 4-benzyl ester (generated from morpholine-2,4-dicarboxylic acid by reaction with benzyl chloroformate under standard protection conditions (such as those described in Greene, T., "Protective Groups in Organic Synthesis," Wiley-interscience, 1999)) is coupled with 2-aminoethylphosphonic acid diethyl ester (commercially available) using standard reagents for the formation of a secondary amide such as dicyclohexylcarbodiimide (DCC) and hydroxybenztriazole (HOBT), in a solvent such as dimethylformamide. Removal of the benzyl carbamate protecting group by hydrogenation over palladium in a solvent such as methanol (as described in Greene, T. *ibid.*) provides the desired product.

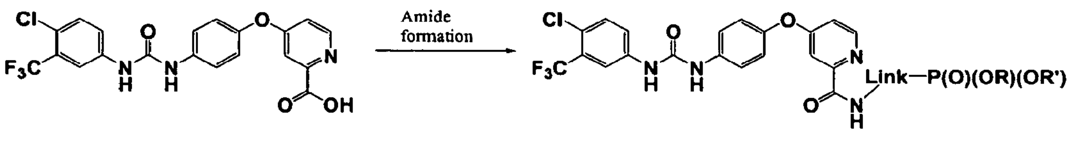
Example 41

Preparation of Representative Compounds of Formulae 31-34

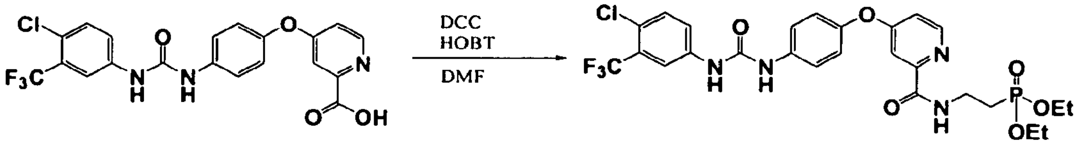
Representative compounds of the invention can be prepared as follows.


Link—P(O)(OR)(OR')
(R'O)(RO)(O)P
Link
Link
P(O)(OR)(OR')
Link—P(O)(OR)(OR')
Cl
F3C

Link = 1-8 atoms, with 2-6 preferred

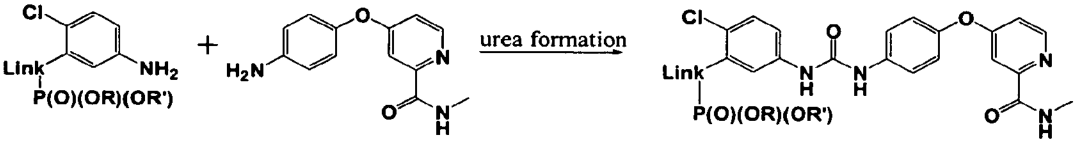

Amide formation
Link—P(O)(OR)(OR')
Cl
F3C
OH

A specific compound of the invention can be prepared as follows:



The acid is coupled with 2-aminoethylphosphonic acid diethyl ester (commercially available) using standard reagents for the formation of a secondary amide such as dicyclohexylcarbodiimide (DCC) and hydroxybenztriazole (HOBT), in a solvent such as dimethylformamide.

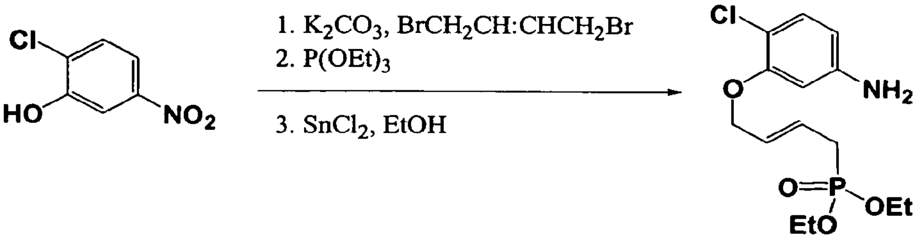
Representative compounds of the invention may also be prepared as follows:



An aniline bearing a phosphonate moiety is coupled with 4-(4-aminophenoxy)-pyridine-2-carboxylic acid methylamide (US 2002/0165394) in the presence of a reagent such as phosgene, in a solvent such as toluene to form a urea (see Bioorg. Med. Chem. Lett., 11:2775 (2001)).

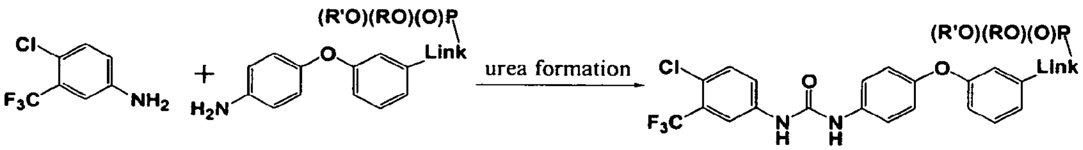
4-(4-Aminophenoxy)-pyridine-2-carboxylic acid methylamide is formed by alkylation of (4-hydroxypridine-2-carboxylic acid methylamide with 4-fluoronitrobenzene with a base such as cesium carbonate in a solvent such as dimethylformamide, followed by reduction of the nitro group with tin(II) chloride in a solvent such as ethanol.

The synthesis of a specific compound of the invention, *e.g.*, a suitable phosphonate-bearing aniline, is illustrated below.

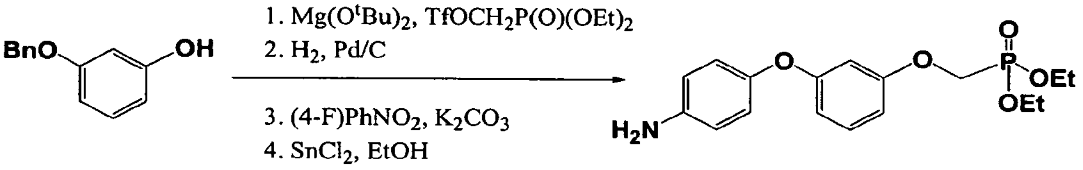


2-Chloro-5-nitrophenol is alkylated with an excess of *E*-1,4-dibromobutene in a solvent such as dimethylformamide in the presence of a base such as potassium carbonate. The monobromide product is heated with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction conditions: see Engel, R., "Synthesis of Carbon-phosphorus Bonds," CRC press, 1988). Finally, the nitro group is reduced with tin(II) chloride in a solvent such as ethanol.

Synthesis of representative compounds of the invention is shown below.

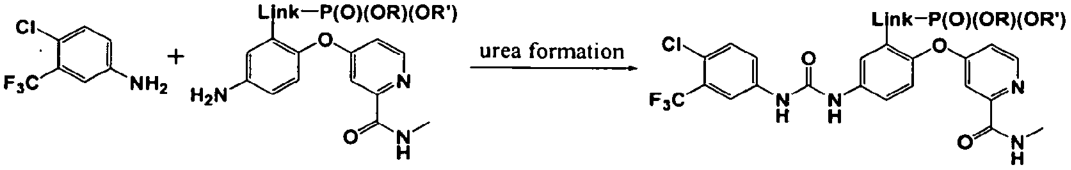


4-Chloro-3-trifluoromethylaniline is coupled with a 4-phenoxy-substituted aniline bearing a phosphonate moiety in a manner similar to that shown in Scheme 2 to form a urea. The synthesis of a specific compound of the invention, *e.g.*, suitable phosphonate-bearing aniline is illustrated below.

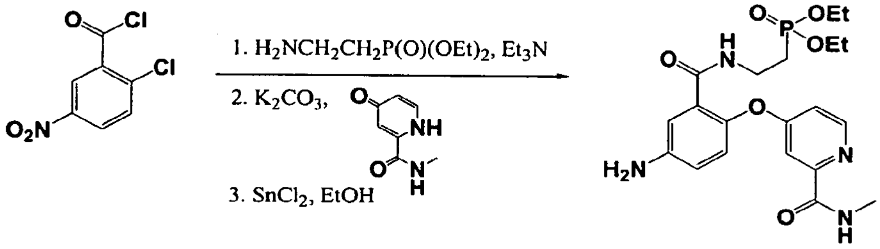


(3-Benzyloxy)phenol is treated with magnesium t-butoxide and diethyl phosphonomethyltriflate (prepared according to Tetrahedron Lett., 27:1477 (1986)) in a solvent such as tetrahydrofuran. The benzyl group is removed by hydrogenation over a catalyst such as palladium on charcoal in a solvent such as methanol as described in Greene, T., "Protective Groups in Organic Synthesis," Wiley-Interscience, 1999, and the resulting phenol is alkylated with 4-fluoronitrobenzene with a base such as potassium carbonate in a solvent such as dimethylformamide. Finally, the nitro group is reduced.

In addition, a representative compound of the invention can be prepared as follows:


Link—P(O)(OR)(OR')
Cl
F₃C
NH₂
H₂N
O
N
O
N
H
urea formation
Link—P(O)(OR)(OR')
Cl
F₃C
O
N
H
N
H
O
N
O
N
H

4-Chloro-3-trifluoromethylaniline is coupled with a 4-phenoxy-substituted aniline bearing a phosphonate moiety in a manner similar to that shown hereinabove to form a urea. The synthesis of a suitable phosphonate-bearing aniline, which is a specific compound of the invention, is illustrated below.

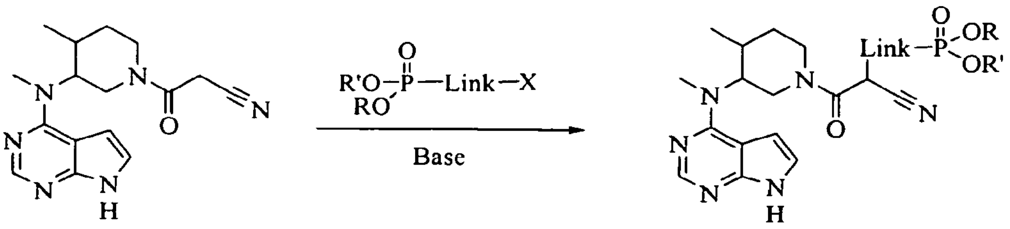

O
Cl
Cl
O₂N
1. H₂NCH₂CH₂P(O)(OEt)₂, Et₃N
2. K₂CO₃,
O
NH
O
N
H
3. SnCl₂, EtOH
O
P
OEt
OEt
H
N
O
O
N
H₂N
O
N
H

2-Chloro-5-nitrobenzoyl chloride is reacted with 2-aminoethylphosphonic acid diethyl ester. Thereafter, displacement of the chloride by reaction with 4-oxo-1,4-dihydro-pyridine-2-carboxylic acid methylamide in the presence of a base such as potassium carbonate in a solvent such as tetrahydrofuran generates the biaryl ether motif, and reduction of the nitro group as in previous examples reveals the aniline ready for coupling in the urea-forming step.

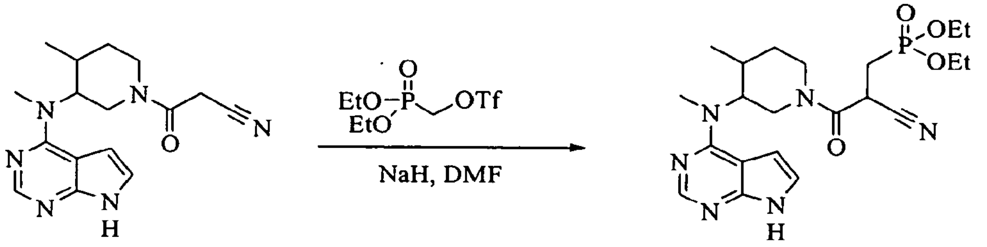
Example 42

Preparation of Representative Compounds of Formulae 35-36

Representative compounds of the invention can be made according to the following:



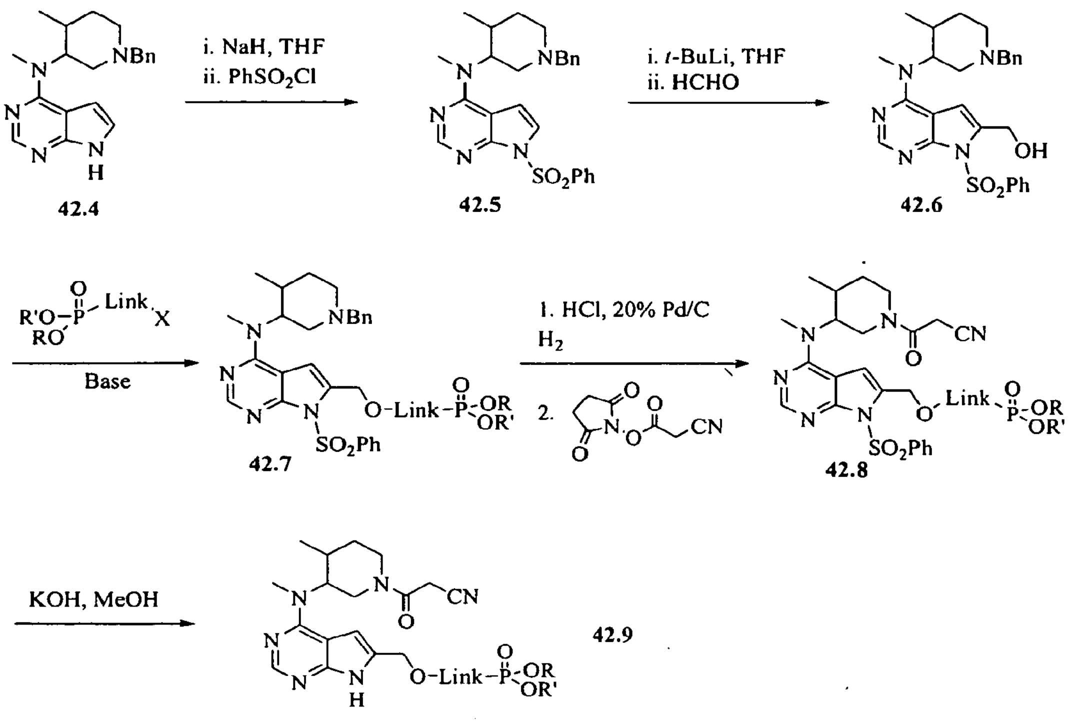
42.1



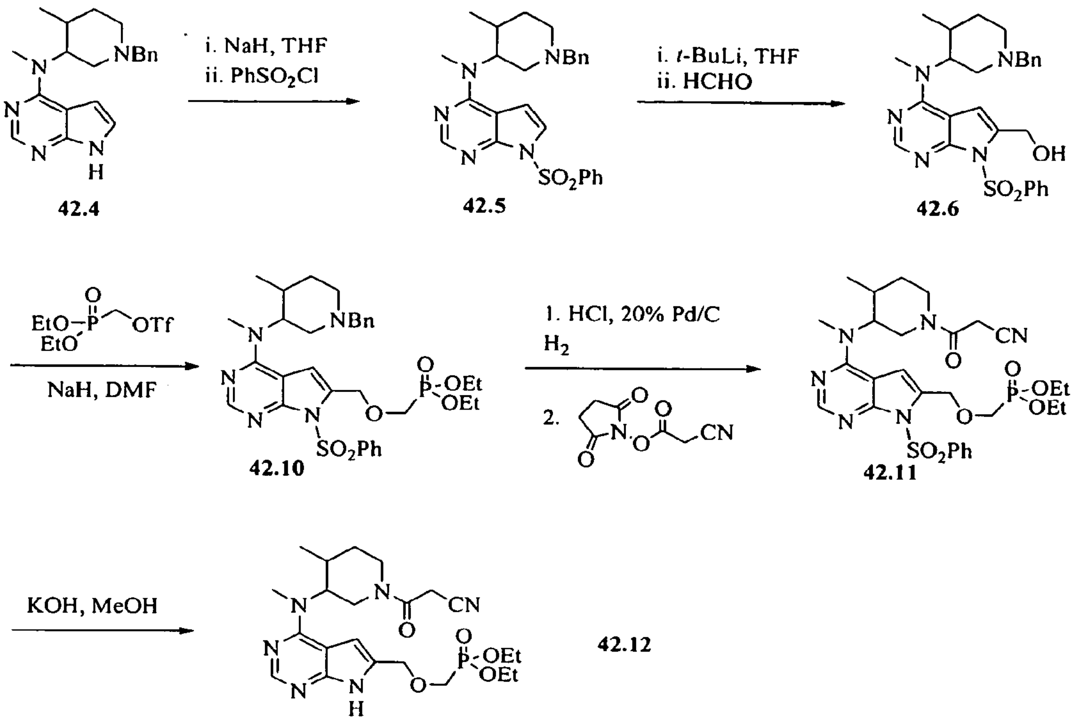
42.3

CP-690,550, 3-{4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl}-3-oxo-propionitrile, can be prepared as described in WO 02,096,909 and WO 03,048,162. Enolate formation at the α-cyanoamide position using over 2 equivalents of base followed by addition of diethyl phosphonomethyltriflate (prepared according to Tetrahedron Lett., 27:1477 (1986)) yields the desired compound **42.1**. A solvent such as THF, DMF or other anhydrous solvents may be used for this reaction. In case the pyrrole nitrogen interferes with the desired alkylation, a protecting group such as BOC may be introduced before the alkylation reaction. Removal of the BOC group can be accomplished by exposure of the reaction product to TFA as described in Greene, T., "Protective Groups in Organic Synthesis," Wiley-Interscience, 1999.

A second series of pro-drugs can be prepared by attaching the phosphonate group on to the pyrrole ring at the 2-position. Compounds such as **42.9** can be made according to the general route outlined below.


42.4
i. NaH, THF
ii. PhSO2Cl
42.5
i. t-BuLi, THF
ii. HCHO
42.6
Base
42.7
1. HCl, 20% Pd/C
H2
2.
42.8
KOH, MeOH
42.9
NBn
SO2Ph
OH
O-Link-P-OR
OR'
CN

Compound **42.4** is prepared according to WO 02,096,909. Protection of the pyrrole nitrogen using a tosyl group is achieved as described in Sakamoto *et al.*, Tetrahedron Lett., 35(18):2919 (1994). Ortho lithiation using *t*-BuLi and quenching with formaldehyde as described in the above reference as well as Seela *et al.*, Chem. Ber., 110(4):1462 (1977) introduces a substituent at the requisite site. The primary alcohol so formed may be used for attachment of the phosphonate moiety *via* ether formation using base and diethyl phosphonomethyltriflate (prepared according to Tetrahedron Lett., 27:1477 (1986)) in an anhydrous solvent. Removal of the benzyl protecting group is achieved using hydrogenolysis conditions. The piperidine nitrogen is then coupled with cyano-acetic acid 2,5-dioxo-pyrrolidine-1-yl ester to provide compound **42.8**. Removal of the tosyl protecting group can be achieved using basic conditions to provide the desired product **42.9**.



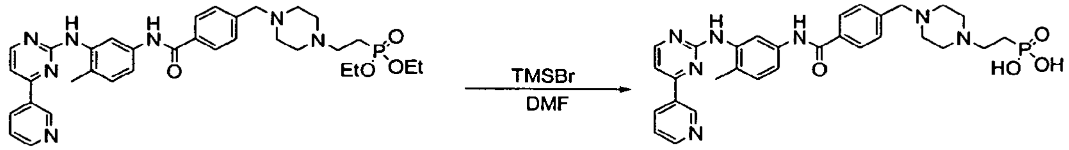
Specifically, as shown above, (1-benzyl-4-methyl-piperidin-3-yl)-methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amine, compound **42.4** (prepared as described in WO 02,096,909) is first protected on the pyrrole nitrogen using a tosyl group. Subsequent formylation using the procedure reported by Sakamoto *et al.*, (Tetrahedron Lett., 35:2919 (1994)) provides compound **42.6**. The primary alcohol is then treated in a solvent such as tetrahydrofuran or dimethylformamide with a base such as sodium hydride. When bubbling ceases, diethyl phosphonomethyltriflate (prepared according to Tetrahedron Lett., 27:1477 (1986)) is added, yielding the desired product **42.10**. Debenzylation of the piperidine nitrogen following by coupling to cyano-acetic acid 2,5-dioxo-pyrrolidine-1-yl ester gives compound **42.4**. Removal of the tosyl protecting group provides the desired pro-drug **42.12**.

Example 43 Preparation of Representative Compounds of Formulae 4-7

Representative compounds of the invention may be prepared as follows:

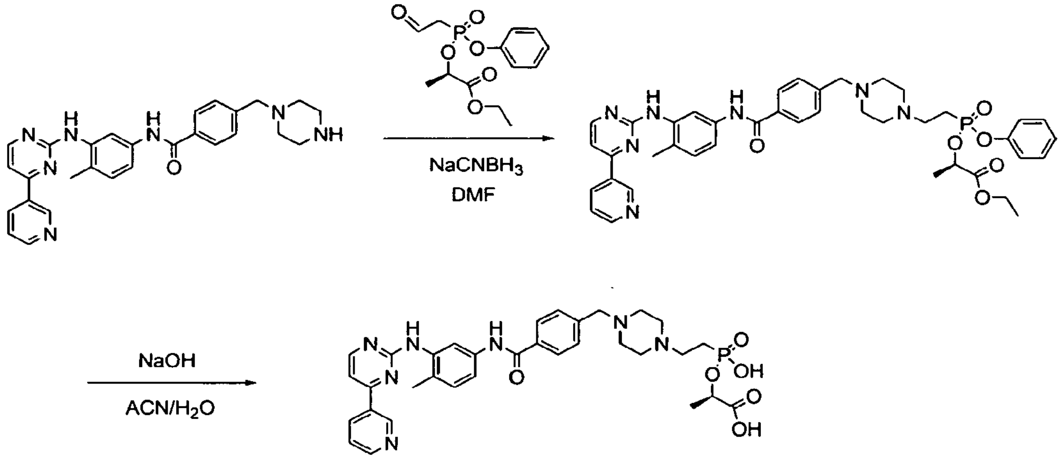
[2-(4-{4-[4-Methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenylcarbamoyl]-benzyl}-piperazin-1-yl)-ethyl]-phosphonic acid diethyl ester

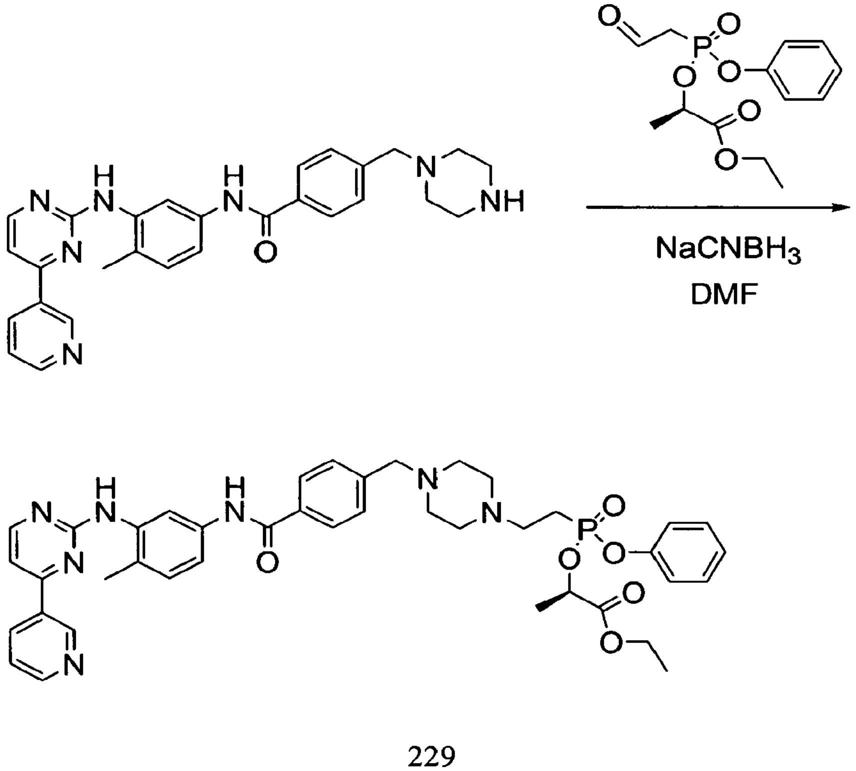
A mixture of *N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-4-piperazin-1-ylmethyl-benzamide (30 mg, 0.06 mmol, Zimmermann et al., *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1221), diethyl 2-bromoethylphosphonate (30 µL, 0.12 mmol) and K_2CO3 (20 mg, 0.16 mmol) in 2.5 mL of DMF was heated at 110 °C for 8 hours when most of the starting materials were consumed as judged by LCMS analysis. The solid material was filtered off. The filtrate was diluted with water and then extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated to dryness. The crude material was purified by silica gel chromatography using 10% MeOH/CH_2Cl_2 to provide 28 mg (55%) of the desired product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, 6H), 1.92-20.3 (m, 4H), 2.35 (s, 3H), 2.5 (bs, 6H), 2.64 (m, 2H), 3.56 (s, 2H), 4.05-4.14 (m, 4H), 7.07(s, 1H), 7.18 (d, 2H, *J*= 5 Hz), 7.30 (dd, 1H, *J*= 6, 8 Hz), 7.33-7.45 (m, 3H), 7.84 (d, 2H, *J*= 8 Hz), 8.01 (s, 1H), 8.51 (dd, 2H, *J*= 4, 9 Hz), 8.58 (d, 1H, *J*= 2 Hz), 8.70 (dd, 1H, *J*= 2, 5 Hz), 9.25 (s, 1H); ^{31}P (121.4 MHz, $CDCl_3$) δ 30.5; MS (*m/z*) 644 $[M+H]^+$.



[2-(4-{4-[4-Methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenylcarbamoyl]-benzyl}-piperazin-1-yl)-ethyl]-phosphonic acid

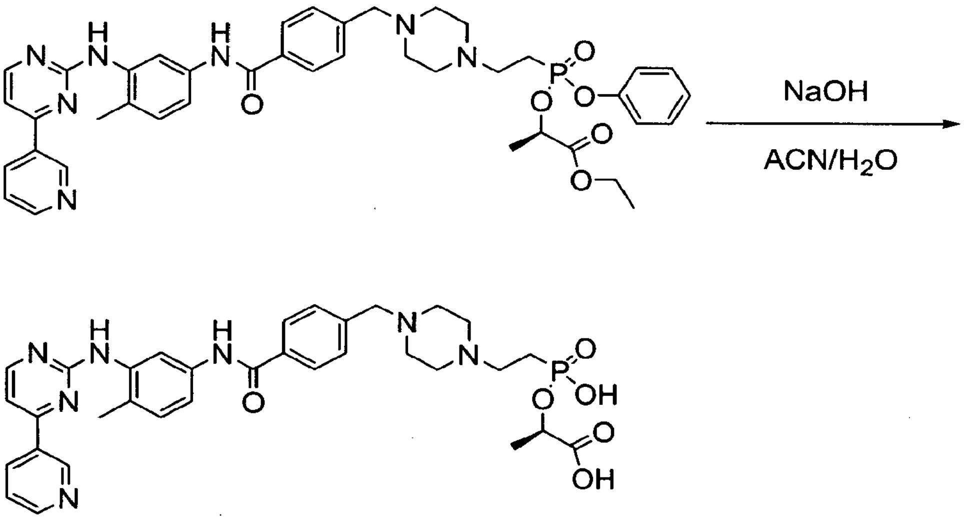
To a solution of [2-(4-{4-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenylcarbamoyl]-benzyl}-piperazin-1-yl)-ethyl]-phosphonic acid diethyl ester (8 mg, 0.012 mmol) in DMF (1 mL) was added TMSBr (15 µL, 0.12 mmol) at room temperature. The reaction was allowed to proceed at room temperature for 14 hours. Another portion of TMSBr (20 µL) was added and heated at 110 °C for 12 hours when completion of the reaction was detected by LCMS. The reaction was cooled down to room temperature and quenched with addition of MeOH. The reaction mixture was dried under reduced pressure and the residue was purified by RP HPLC using a C18 column with a gradient of H_2O- Acetonitrile (5-100%) over 20 minutes to provide 4.2 mg (50%) of the product as mono-TFA salt. ^1H NMR (300 MHz, CD_3OD) δ 1.80-1.84 (m, 2H), 2.08-2.02 (m, 2H), 2.23 (s, 3H), 3.07 (bs, 4H), 3.30-3.32 (2H, possible overlap with solvent), 3.89 (m, 2H), 4.01 (s, 2H), 6.87 (s, 1H), 7.23-7.3 (m, 3H), 7.52-7.60 (m, 3H), 8.01 (d, 2H, *J*= 8 Hz), 8.08 (dd, 1H, *J*= 2, 5 Hz), 8.30 (s, 1H), 8.58 (d, 1H, *J*= 5 Hz), 8.89 (d, 1H, *J*= 2 Hz), 9.22 (dd, 1H, *J*= 2, 5 Hz), 9.63 (s, 1H); ^{31}P (121.4 MHz, CD_3OD) δ 21.9 ; MS (*m/z*) 588 $[M+H]^+$.





2-{[2-(4-{4-[4-Methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenylcarbamoyl]-benzyl}-piperazin-1-yl)-ethyl]-phenoxy-phosphinoyloxy}-propionic acid ethyl ester

A solution of *N*-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-4-piperazin-1-ylmethyl-benzamide (20 mg, 0.04 mmol) and 2-[(2-oxo-ethyl)-phenoxy-phosphinoyloxy]-propionic acid ethyl ester (60 mg, 0.2 mmol) in 1% Acetic Acid/DMF (1.5 mL) solution was stirred at room temperature for 7 hours followed by an addition of $NaCNBH_3$ (30 mg, 0.24 mmol). The resulting mixture was stirred for additional 30 min when completion of the reaction was observed by LCMS. After evaporation of solvent, the residue was taken up in CH_2Cl_2 and then extracted with saturated aqueous $NaHCO_3$. The organic extracts were dried *in vacuo* and the residue was purified by silica gel chromatography using MeOH-CH_2Cl_2 (7%) to afford 8 mg (26 %) of the product. ^{31}P NMR (121.4 MHz, $CDCl_3$) δ 27.2, 28.6 ; MS (*m/z*) 764 $[M+H]^+$.



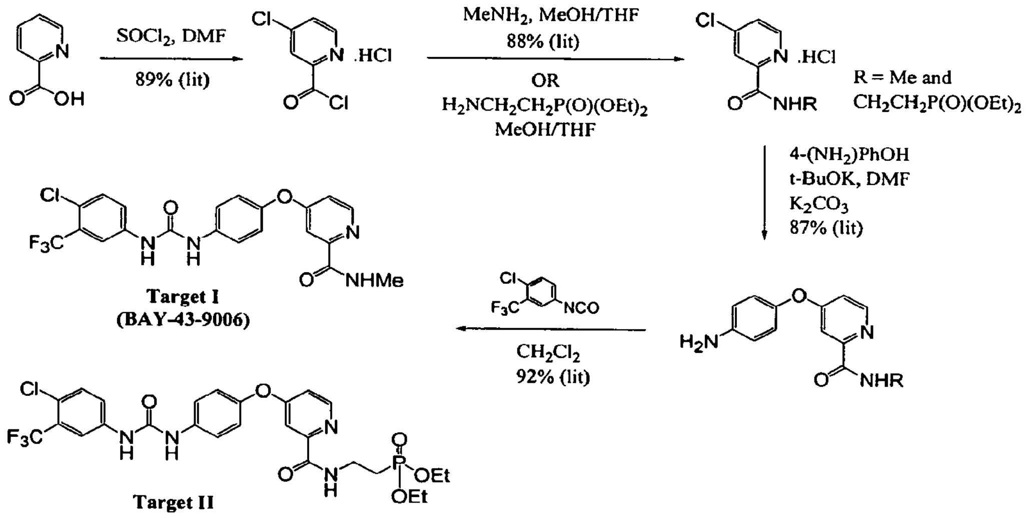
2-{Hydroxy-[2-(4-{4-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenylcarbamoyl]-benzyl}-piperazin-1-yl)-ethyl]-phosphinoyloxy}-propionic acid

To a solution of 2-{[2-(4-{4-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-phenylcarbamoyl]-benzyl}-piperazin-1-yl)-ethyl]-phenoxy-phosphinoyloxy}-propionic acid ethyl ester (6 mg, 0.008 mmol) in 2:1

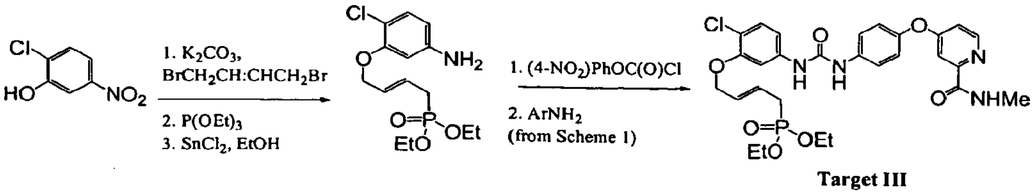
acetonitrile/water (0.3 mL) was added 1N NaOH (50 µL, 0.048 mmol). The solution was allowed to stir at room temperature for 1 hour when completion of the reaction was observed by LCMS. The reaction was acidified by 1N HCl (50 µL) solution and purified by RP HPLC using a C18 column with a gradient of H_2O- Acetonitrile (5-100%) over 20 minutes to provide 2 mg (38%) of the product. ^{1}H NMR (300 MHz, CD_3OD) δ 1.51 (d, 3H, *J*= 7 Hz), 2.04 (m, 2H), 2.33 (s, 3H), 2.96 (bs, 4H), 3.31 (m, 2H), 3.4 (bs, 4H), 3.89 (s, 2H), 4.88 (1H, possible overlap with solvent), 7.30 (m, 2H), 7.48-7.57 (m, 4H), 7.96-7.99 (m, 4H), 8.32 (s, 1H), 8.56 (d, 1H, *J*= 5 Hz), 8.86 (d, 1H, *J*= 2 Hz), 9.10 (dd, 1H, *J*= 2, 5 Hz), 9.59 (s, 1H); ^{31}P (121.4 MHz, CD_3OD) δ 20.0 ; MS (*m/z*) 660 $[M+H]^+$.

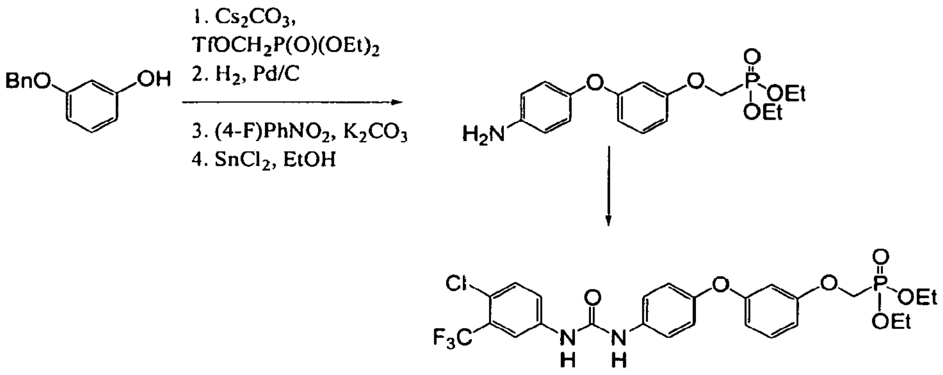
Example 44 Preparation of Representative Compounds of Formulae 31-34

Preparation of representative compounds of the invention can be as discussed below.


SOCl2, DMF
89% (lit)
.HCl
MeNH2, MeOH/THF
88% (lit)
OR
H2NCH2CH2P(O)(OEt)2
MeOH/THF
.HCl
NHR
R = Me and
CH2CH2P(O)(OEt)2
4-(NH2)PhOH
t-BuOK, DMF
K2CO3
87% (lit)
NHMe
Target I
(BAY-43-9006)
NCO
CH2Cl2
92% (lit)
H2N
NHR
Target II
OEt
OEt

In addition, representative compounds of the invention can be synthesized as follows:

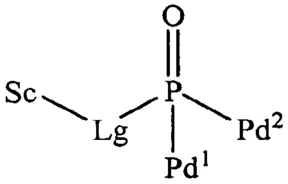

1. K2CO3,
BrCH2CH:CHCH2Br
2. P(OEt)3
3. SnCl2, EtOH
NH2
1. (4-NO2)PhOC(O)Cl
2. ArNH2
(from Scheme 1)
NHMe
Target III


BnO
OH
1. Cs2CO3,
TfOCH2P(O)(OEt)2
2. H2, Pd/C
3. (4-F)PhNO2, K2CO3
4. SnCl2, EtOH
H2N
O
O
O
P
OEt
OEt
Cl
F3C
N
H
N
H
O
O
O
O
P
OEt
OEt

Target IV

Example 45

By way of example and not limitation, embodiments of the invention are named below in tabular format (Table 106). These embodiments are of the general formula "MBF":



MBF

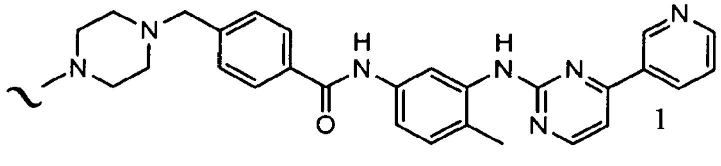
Each embodiment of MBF is depicted as a substituted nucleus (Sc). Sc is described in formula **1-36** herein, wherein A^0 is the point of covalent attachment of Sc to Lg, as well as in Tables 1.1 to 1.5 below. For those embodiments described in Table 106, Sc is a nucleus designated by a number and each substituent is designated in order by letter or number. Tables 1.1 to 1.5 are a schedule of nuclei used in forming the embodiments of Table 106. Each nucleus (Sc) is given a number designation from Tables 1.1 to 1.5, and this designation appears first in each embodiment name. Similarly, Tables 10.1 to 10.19 and 20.1 to 20.36 list the selected linking groups (Lg) and prodrug (Pd^1 and Pd^2) substituents, again by letter or number designation, respectively. Accordingly, a compound of the formula MBF includes compounds having Sc groups based on formula **1-36** herein as well as compounds according to Table 100 below. In all cases, compounds of the formula MBF have groups Lg, Pd^1 and Pd^2 setforth in the Tables below.

Accordingly, each named embodiment of Table 106 is depicted by a number designating the nucleus from Table 1.1-1.5, followed by a letter designating the linking group (Lg) from Table 10.1-10.19, and two numbers designating the two prodrug groups (Pd^1 and Pd^2) from Table 20.1-20.36. In graphical tabular form, each embodiment of Table 106 appears as a name having the syntax:

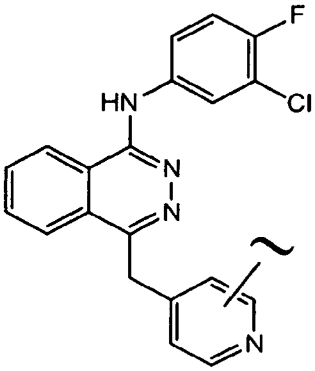
$$Sc.Lg.Pd^1.Pd^2$$

Each Sc group is shown having a tilda ("~"). The tilda is the point of covalent attachment of Sc to Lg. Q^1 and Q^2 of the linking groups (Lg), it should be understood, do not represent groups or atoms but are simply connectivity designations. Q^1 is the site of the covalent bond to the nucleus (Sc) and Q^2 is the site of the covalent bond to the phosphorous atom of formula MBF. Each prodrug group (Pd^1 and Pd^2) are covalently bonded to the phosphorous atom of MBF at the tilda symbol ("~"). Some embodiments of Tables 10.1-10.19 and 20.1-20.36 may be designated as a combination of letters and numbers (Table 10.1-10.19) or number and letter (Table 20.1-20.36). For example there are Table 10 entries for BJ1 and BJ2. In any event, entries of Table 10.1-10.19 always begin with a letter and those of Table 20.1-20.36 always begin with a number. When a nucleus (Sc) is shown enclosed within square brackets ("[]") and a covalent bond extends outside the brackets, the point of covalent attachment of Sc to Lg may be at any substitutable site on SC. Selection of the point of attachment is described herein. By way of example and not limitation, the point of attachment is selected from those depicted in the schemes and examples.

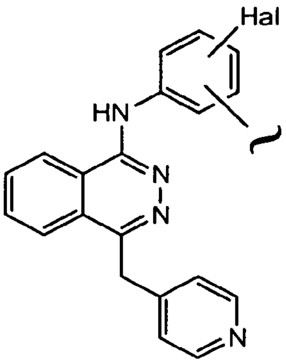
Table 1.1



1



2



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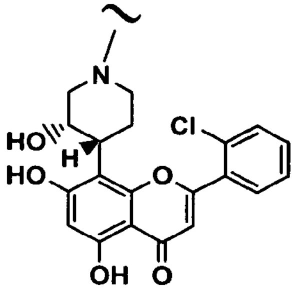
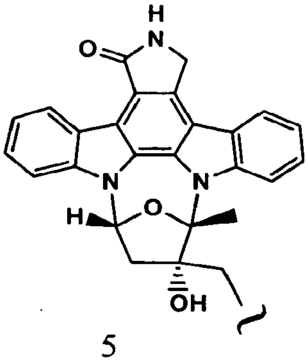


4

Table 1.2



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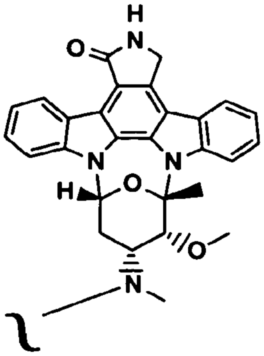
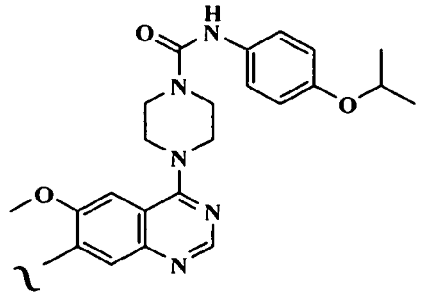


6

Table 1.3



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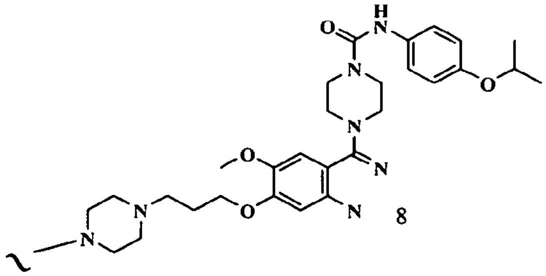

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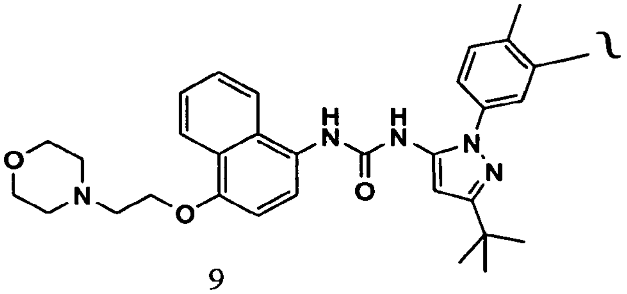

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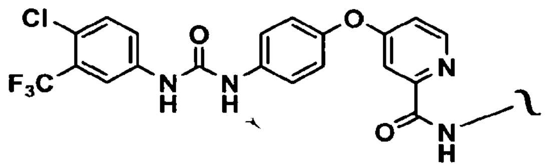
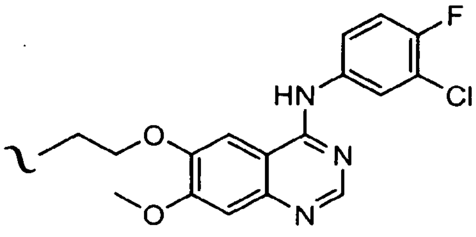


10

Table 1.4



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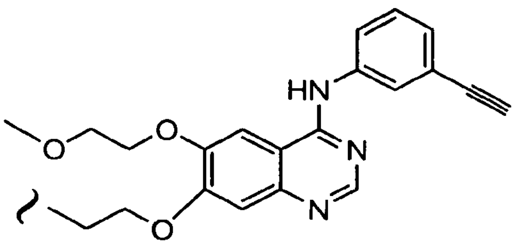
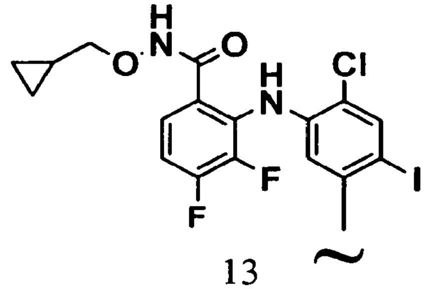


12

Table 1.5



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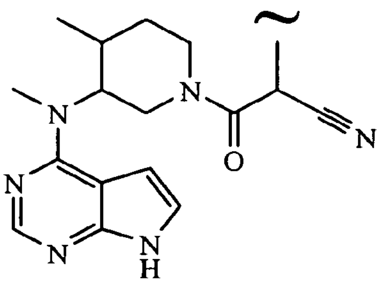
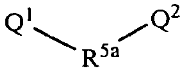
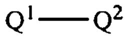


14

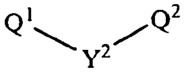
Table 10.1



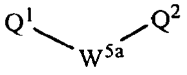
A



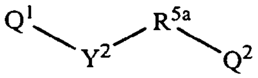
B



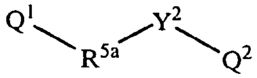
C



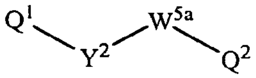
D



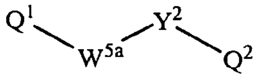
E



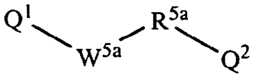
F



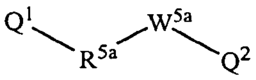
G



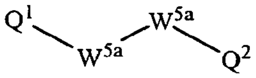
H


Q1
W5a
R5a
Q2

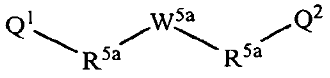
I


Q1
R5a
W5a
Q2

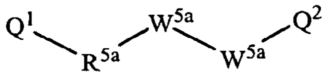
J


Q1
W5a
W5a
Q2

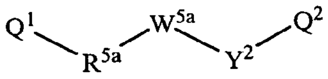
K


Q1
R5a
W5a
R5a
Q2

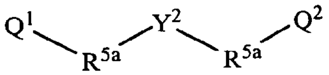
L


Q1
R5a
W5a
W5a
Q2

M

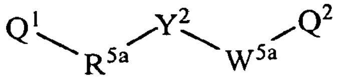

Q1
R5a
W5a
Y2
Q2

N

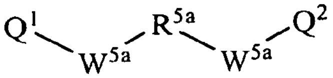

Q1
R5a
Y2
R5a
Q2

O

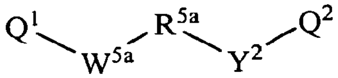
Table 10.2


Q¹
R⁵ᵃ
Y²
W⁵ᵃ
Q²

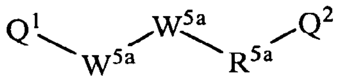
P


Q¹
W⁵ᵃ
R⁵ᵃ
W⁵ᵃ
Q²

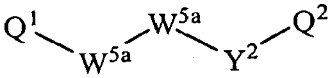
Q


Q¹
W⁵ᵃ
R⁵ᵃ
Y²
Q²

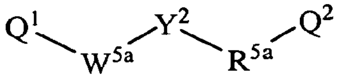
R


Q¹
W⁵ᵃ
W⁵ᵃ
R⁵ᵃ
Q²

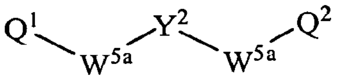
S


Q¹
W⁵ᵃ
W⁵ᵃ
Y²
Q²

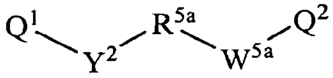
T


Q¹
W⁵ᵃ
Y²
R⁵ᵃ
Q²

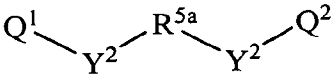
U


Q¹
W⁵ᵃ
Y²
W⁵ᵃ
Q²

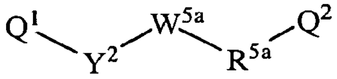
V


Q¹
Y²
R⁵ᵃ
W⁵ᵃ
Q²

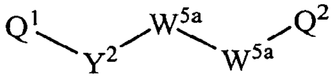
W


Q¹
Y²
R⁵ᵃ
Y²
Q²

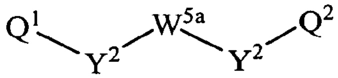
X


Q¹
Y²
W⁵ᵃ
R⁵ᵃ
Q²

Y

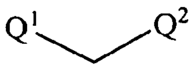

Q¹
Y²
W⁵ᵃ
W⁵ᵃ
Q²

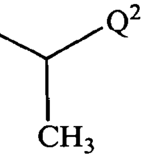
Z

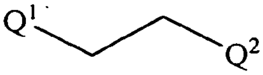

Q¹
Y²
W⁵ᵃ
Y²
Q²

AA

Table 10.3


AB


AC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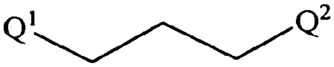
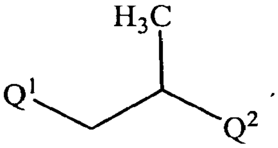
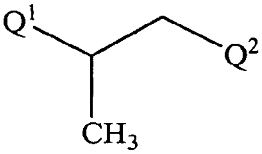
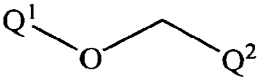
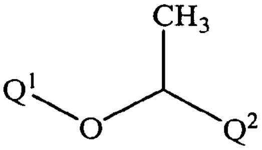
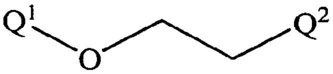

AE

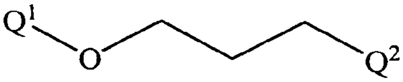

AF


AG


AH


AI


AJ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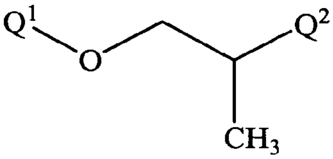
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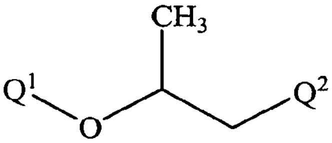
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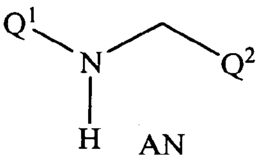
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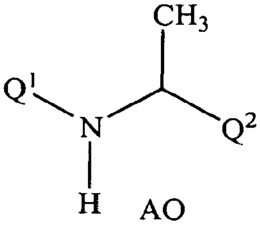
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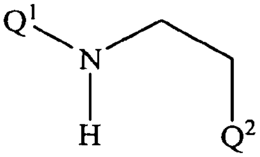
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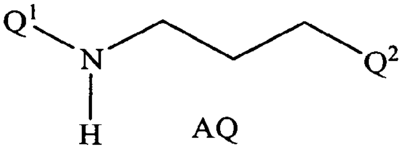
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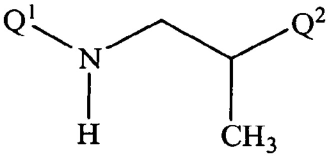
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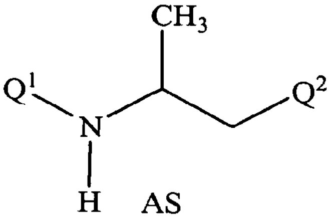
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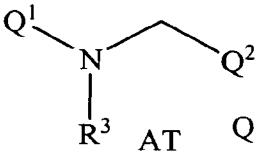
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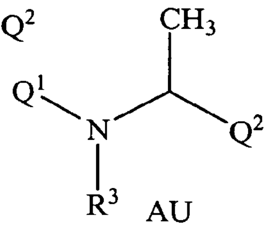
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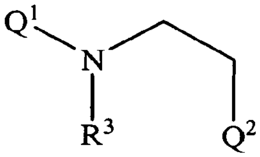
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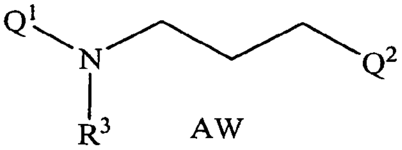
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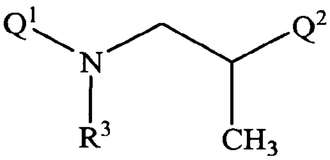
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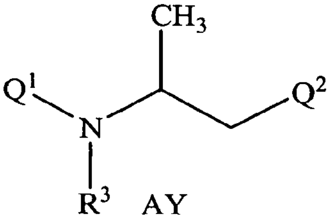
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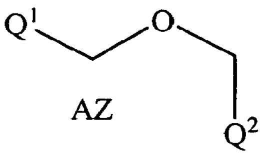
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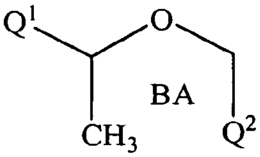
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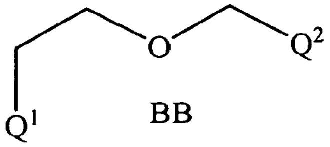
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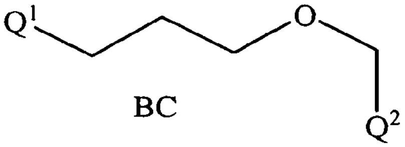
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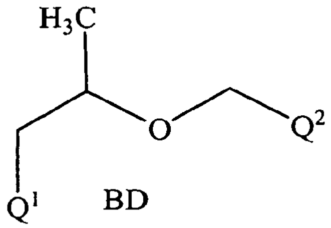
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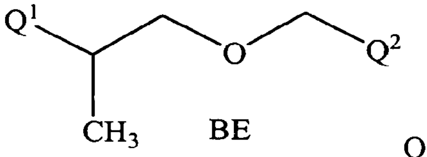
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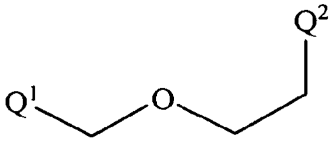
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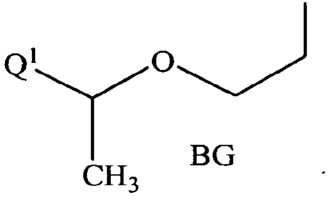
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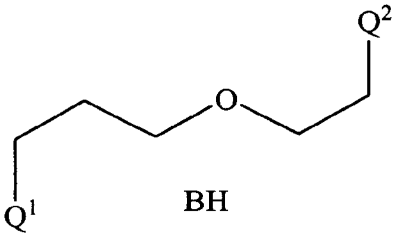
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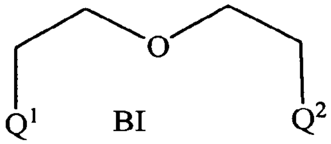
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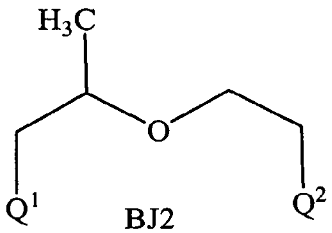
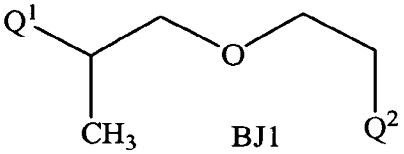

BJ2


BJ1

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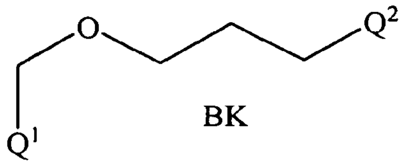

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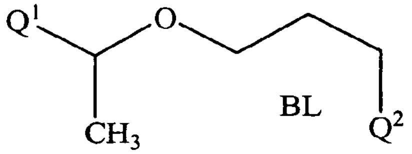
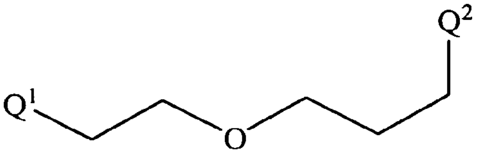


BL



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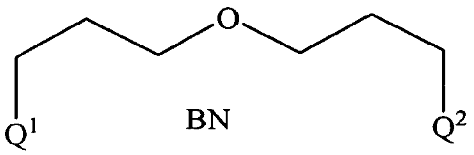

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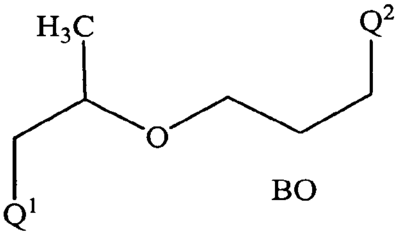
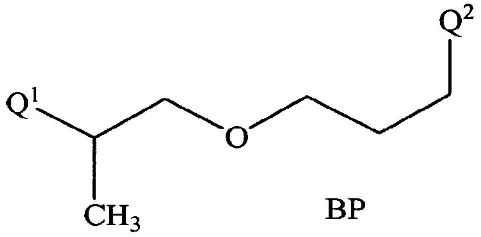


BO



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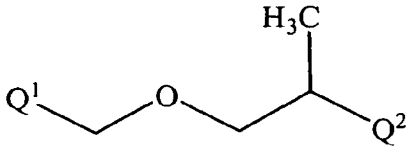

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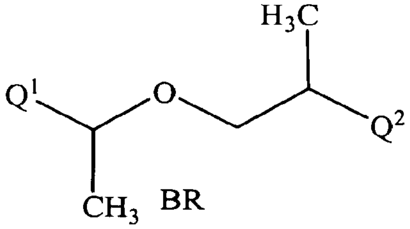
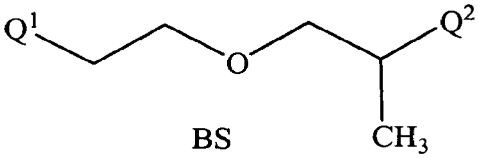

H3C
Q1
O
Q2
CH3

BR



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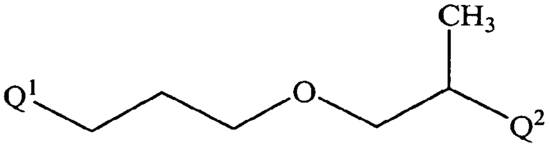

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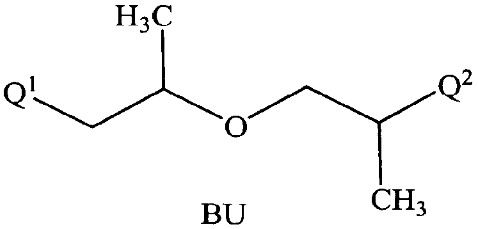
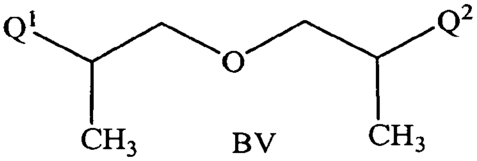
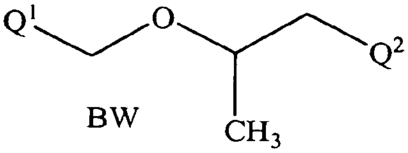

H3C
Q1
O
Q2
CH3

BU


Q1
Q2
O
CH3
CH3

BV

Table 10.8



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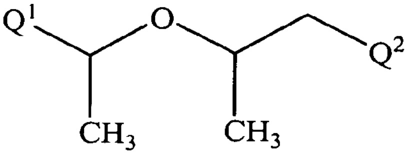
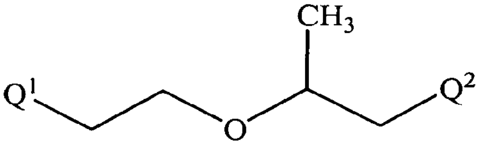

Q1
O
Q2
CH3
CH3

BX



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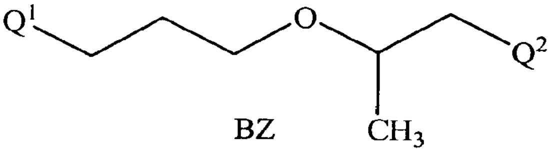

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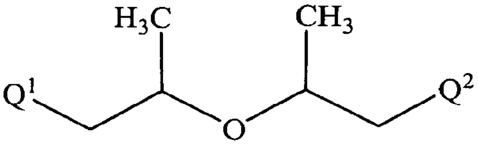
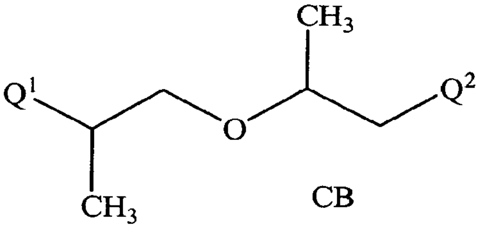
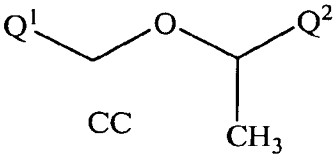

H3C
CH3
Q1
Q2
O

CA


CH3
Q1
Q2
O
CH3

CB

Table 10.9



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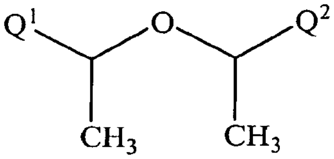
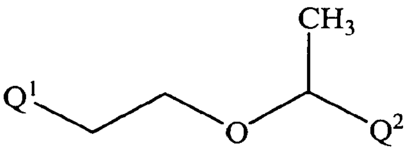

Q1
O
Q2
CH3
CH3

CD



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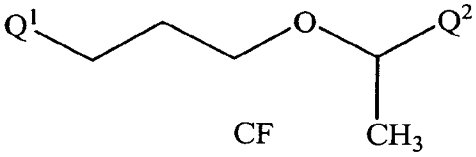

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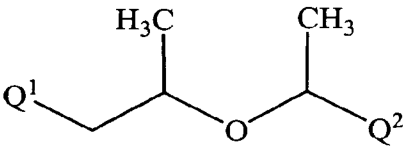
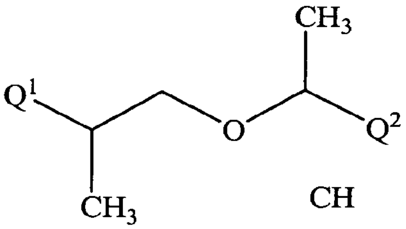
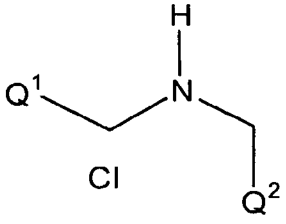

H3C
CH3
Q1
O
Q2

CG


CH3
Q1
O
Q2
CH3

CH

Table 10.10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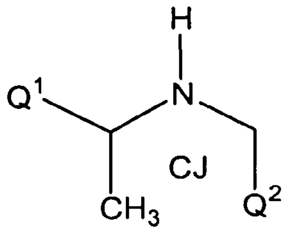
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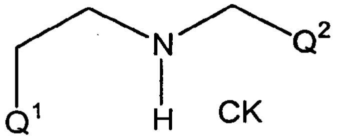
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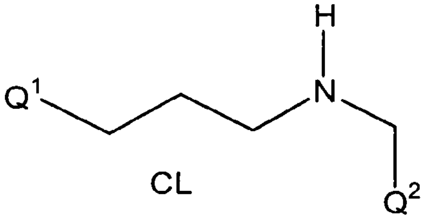
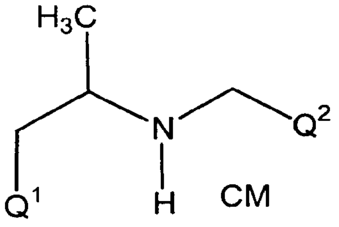

CL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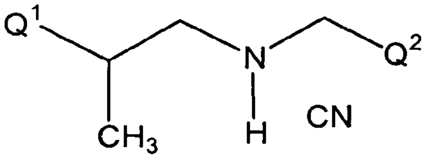
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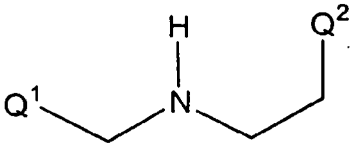

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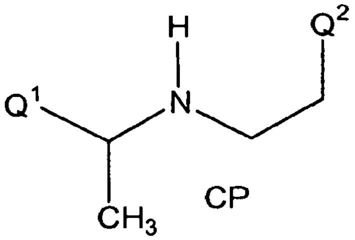

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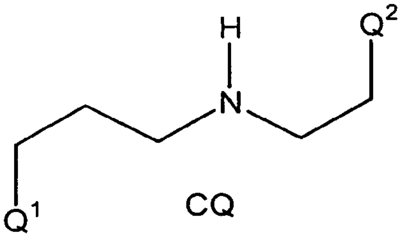

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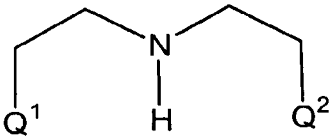

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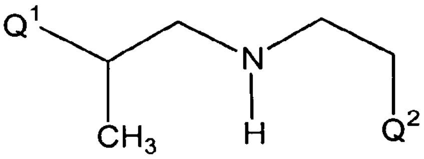

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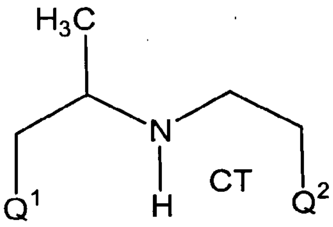

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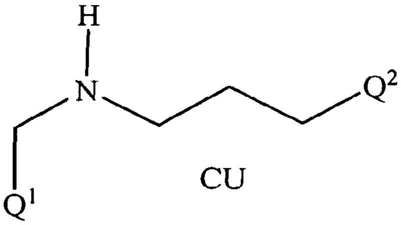

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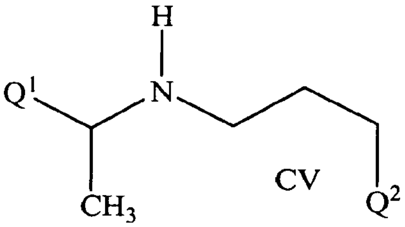

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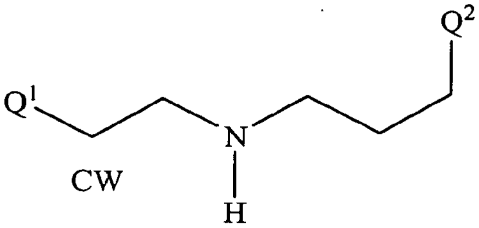

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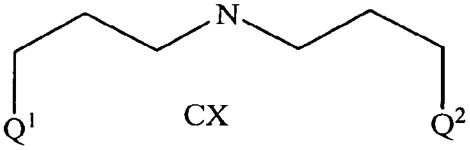

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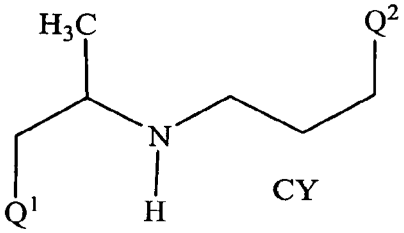

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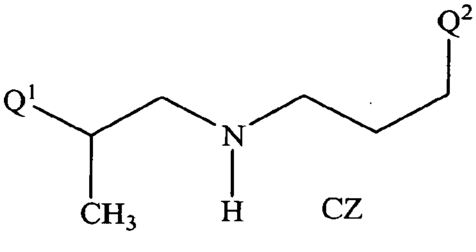

CZ

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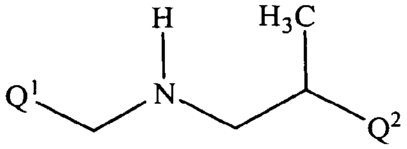

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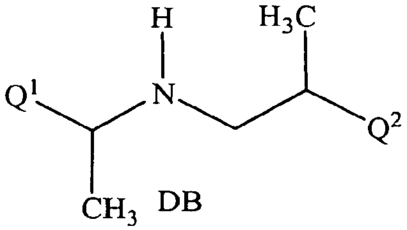
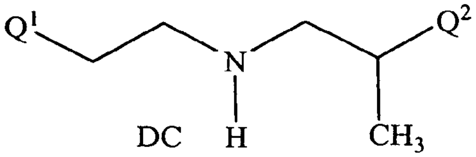
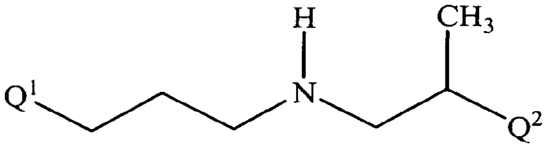

H
H$_3$C
Q^1
N
Q^2
CH$_3$

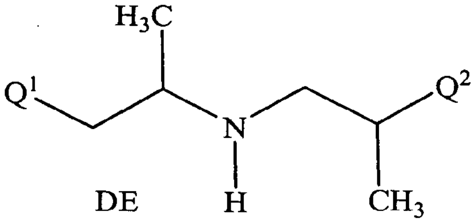
DB



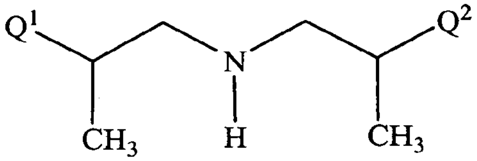
DC



DD

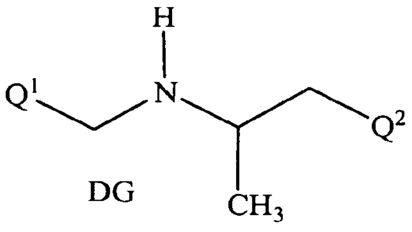

H$_3$C
Q^1
Q^2
N
H
CH$_3$

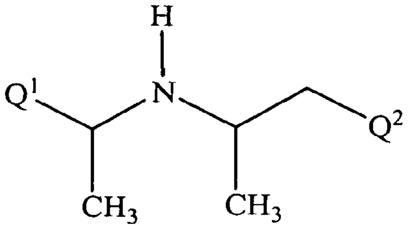
DE


Q^1
Q^2
N
CH$_3$
H
CH$_3$

DF

Table 10.13


DG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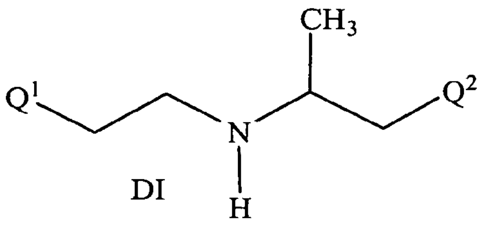
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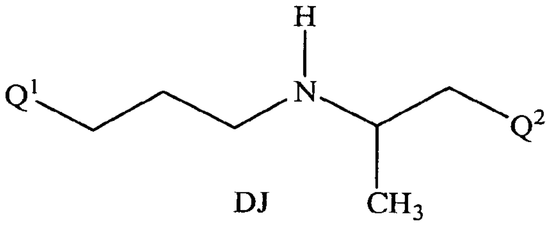
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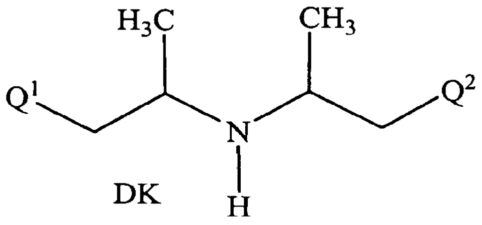
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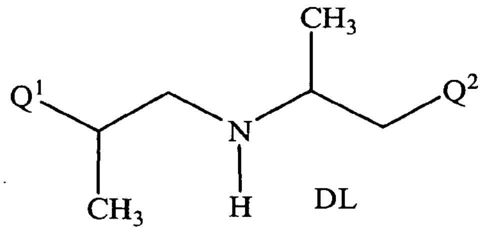
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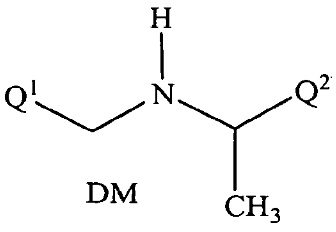
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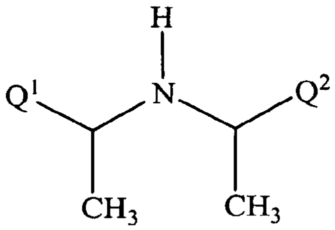
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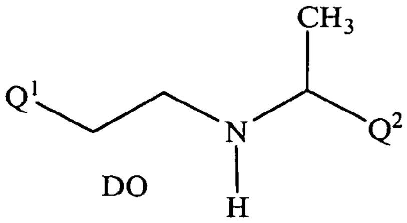
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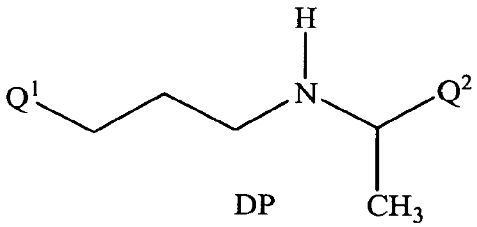
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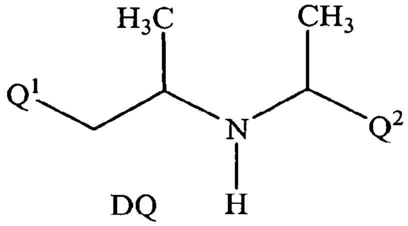
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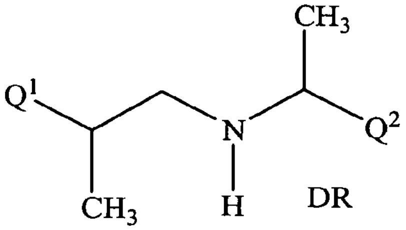
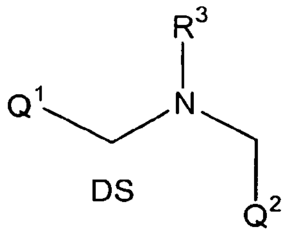

DR

Table 10.15



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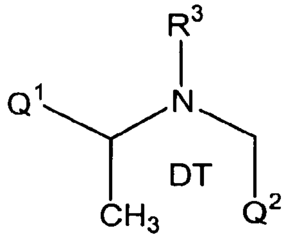
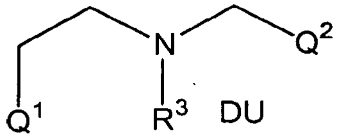


DT



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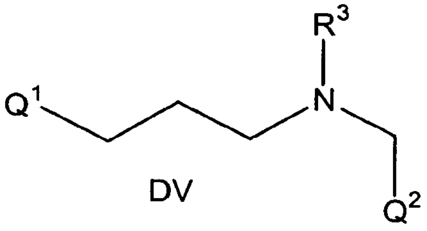
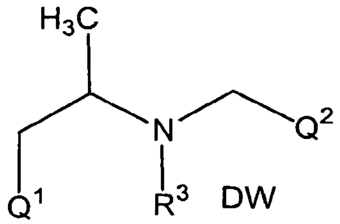


DV



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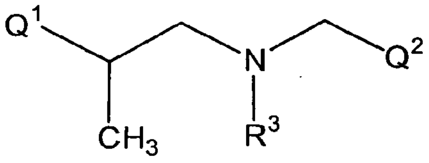

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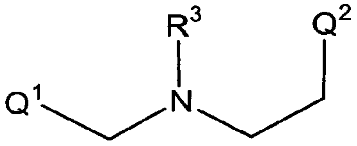

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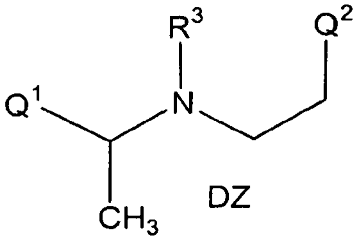

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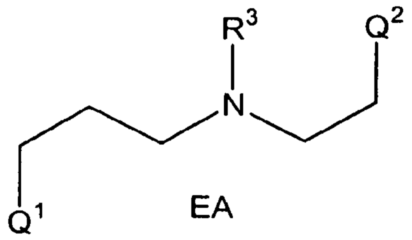

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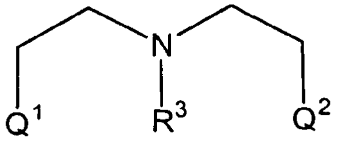

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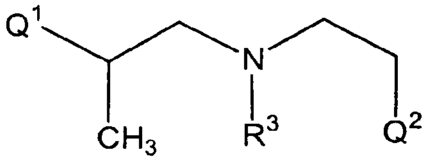
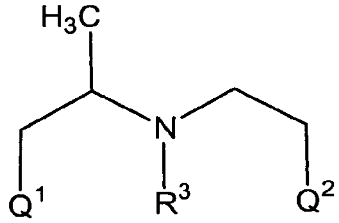
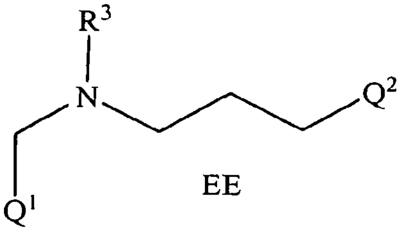

Q1
N
CH3
R3
Q2

EC


H3C
N
Q1
R3
Q2

ED

Table 10.16



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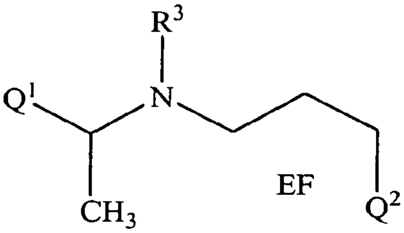

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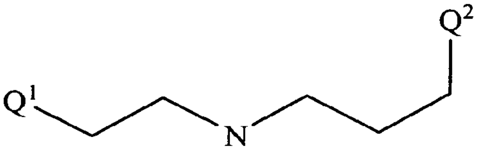

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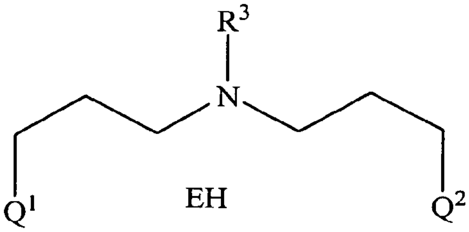
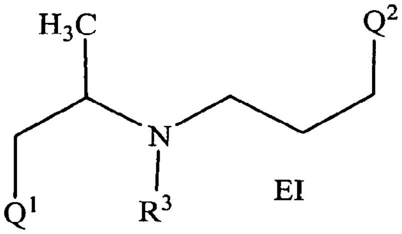


EH



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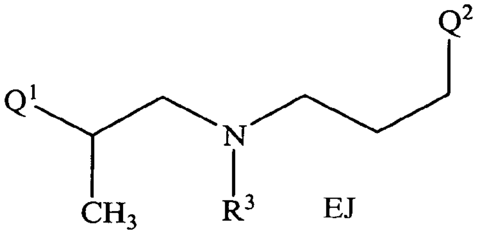
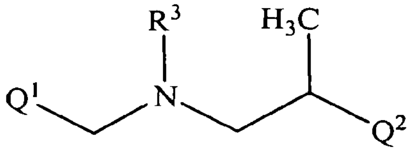
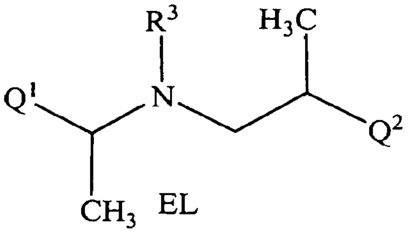


EJ

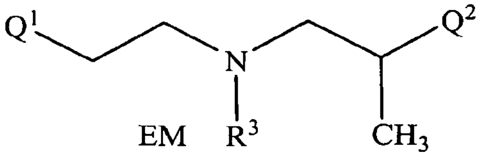
Table 10.17


R3
H3C
Q1
N
Q2

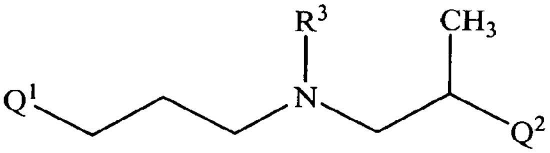
EK


R3
H3C
Q1
N
Q2
CH3

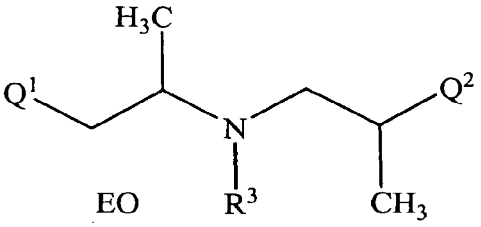
EL


Q1
Q2
N
R3
CH3

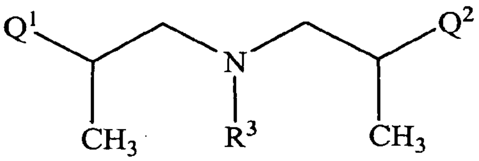
EM


R3
CH3
Q1
N
Q2

EN

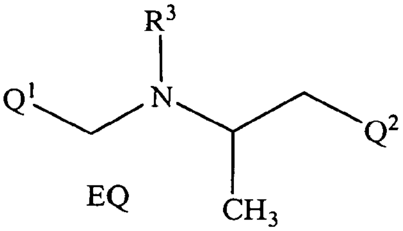

H3C
Q1
Q2
N
R3
CH3

EO


Q1
Q2
N
CH3
R3
CH3

EP

Table 10.18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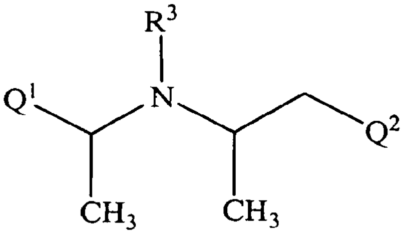
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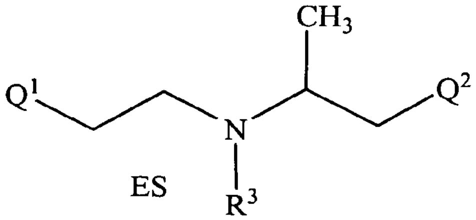
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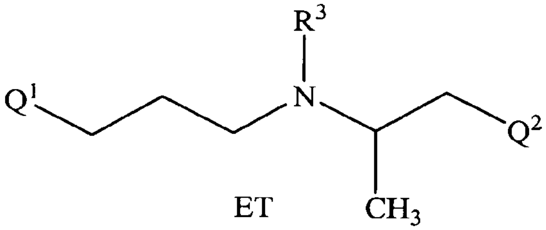
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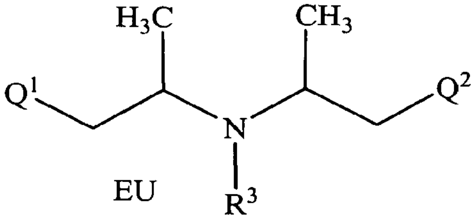
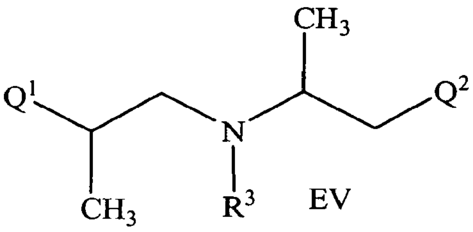

EU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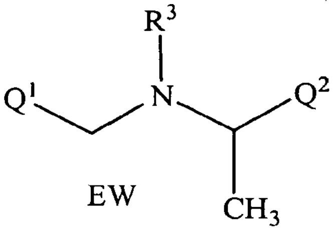
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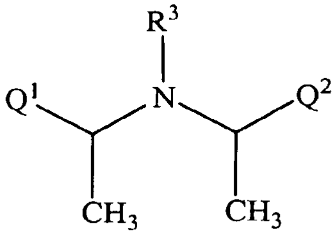
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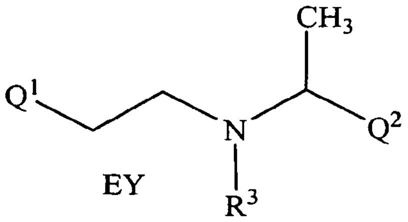
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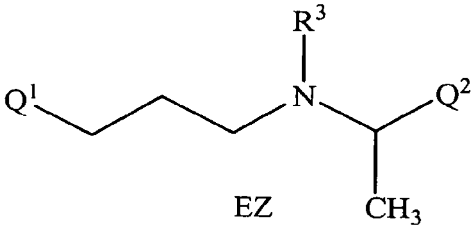
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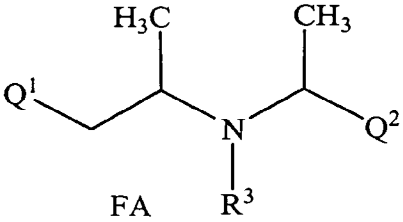
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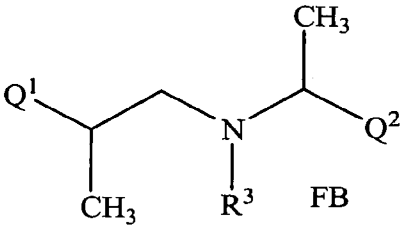
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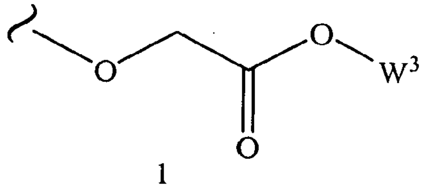

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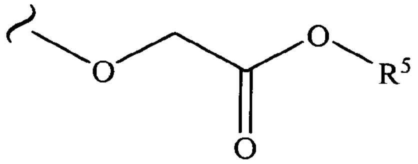

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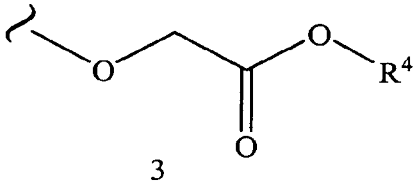

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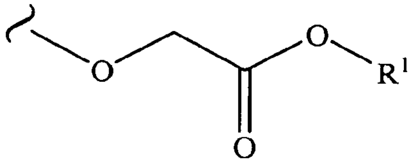

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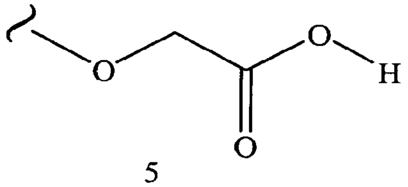

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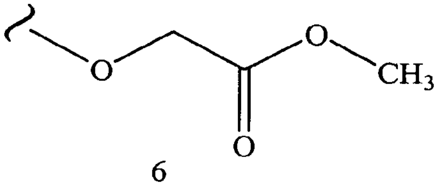

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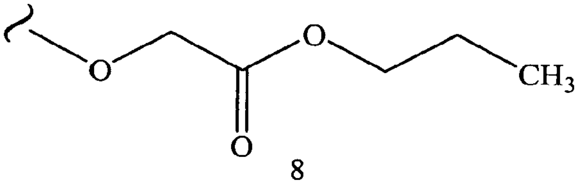

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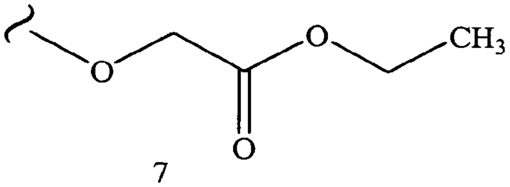

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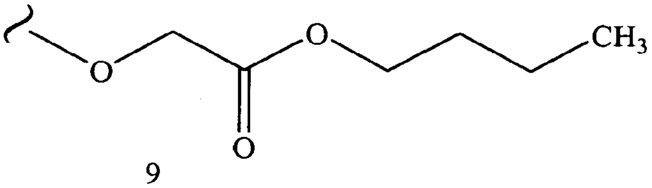

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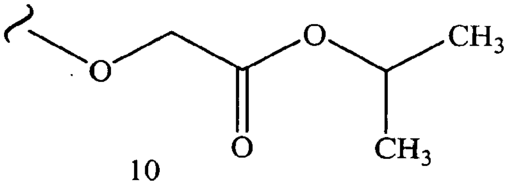

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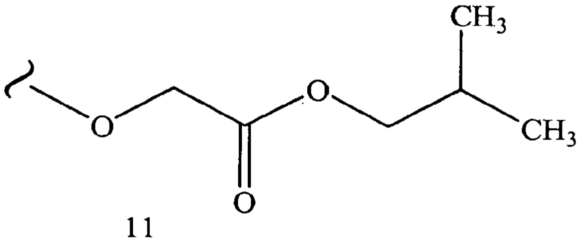

11

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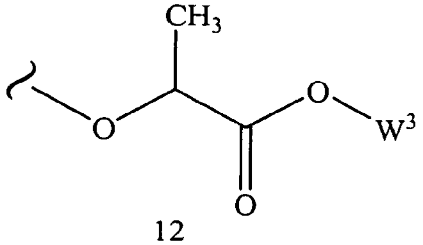
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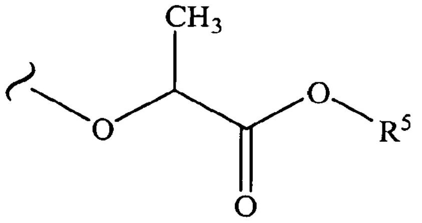
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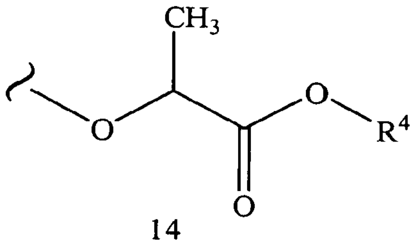
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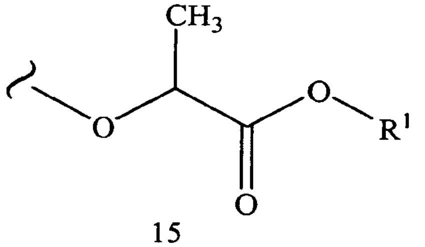
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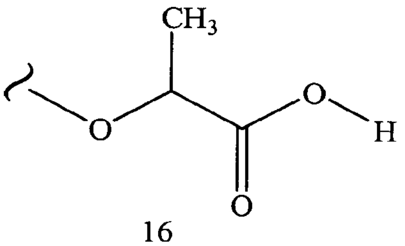
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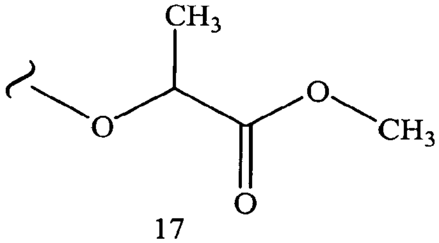
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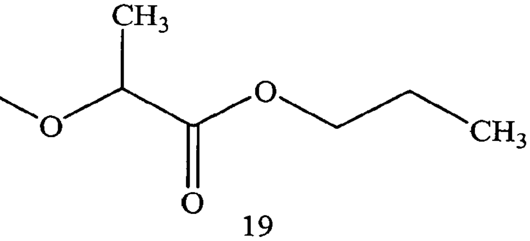
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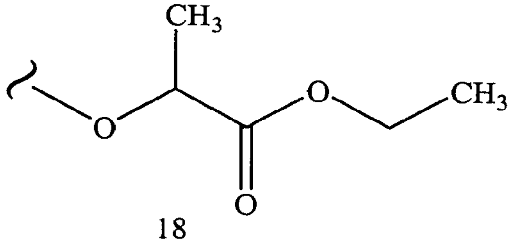
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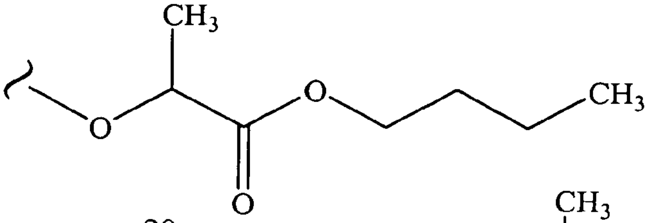

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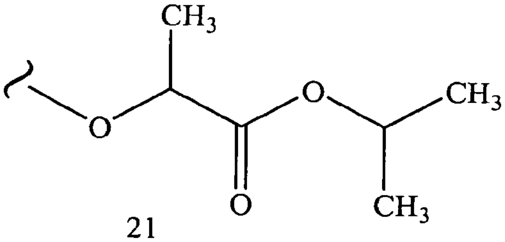

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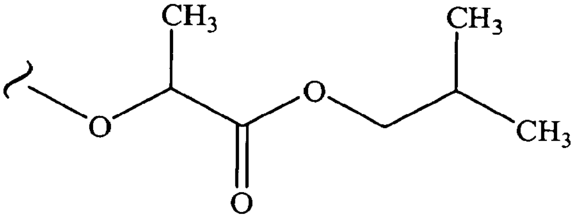

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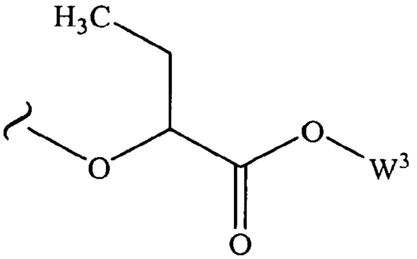
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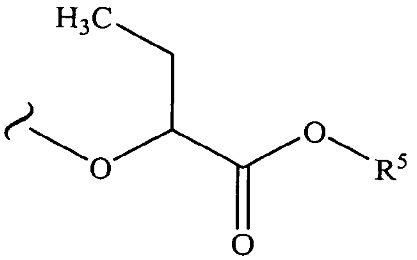
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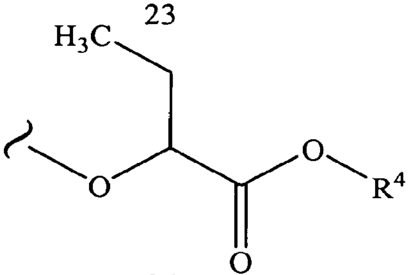
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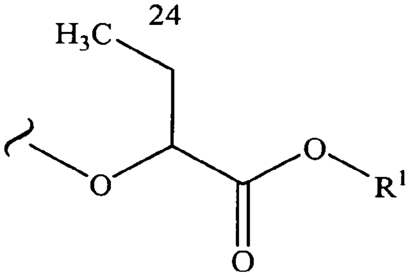
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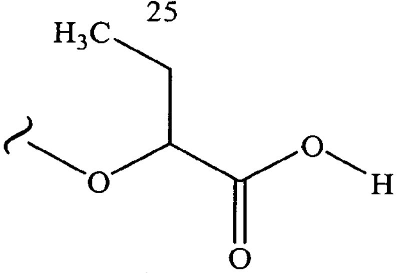
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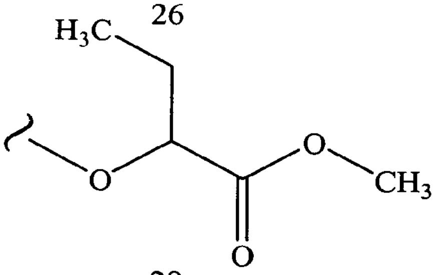
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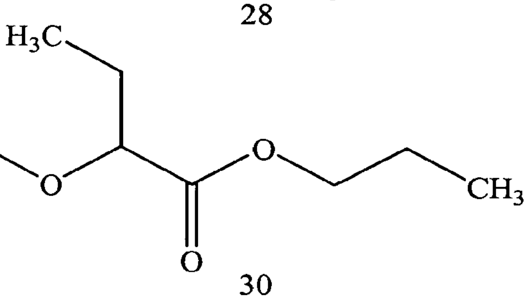
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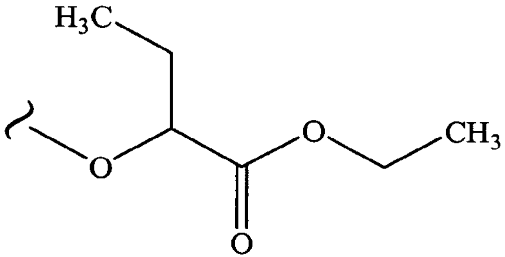
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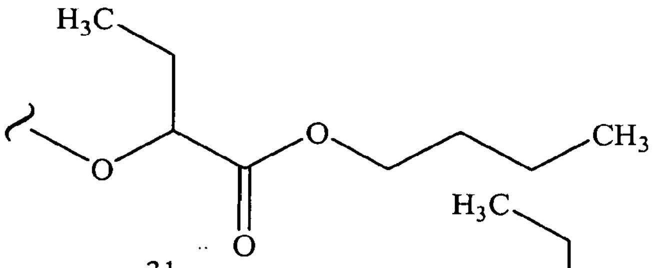

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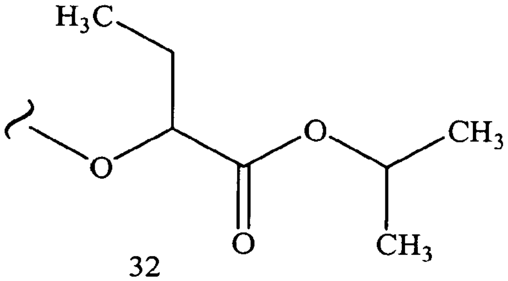
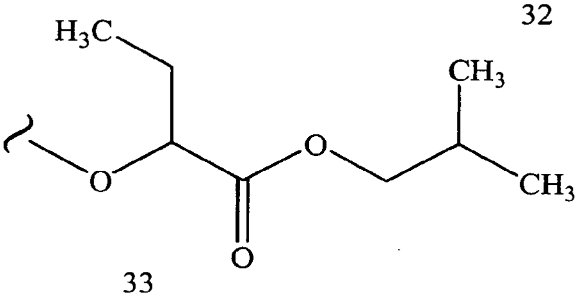

H$_3$C
O
O
O
CH$_3$
CH$_3$

32


H$_3$C
CH$_3$
O
O
O
CH$_3$

33

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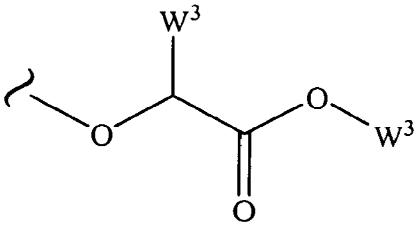

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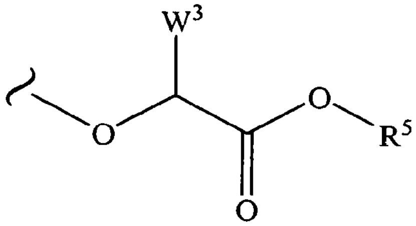

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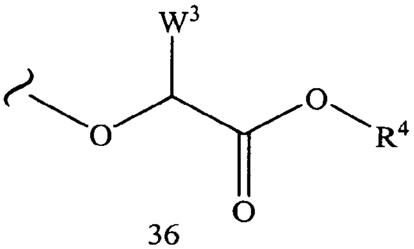

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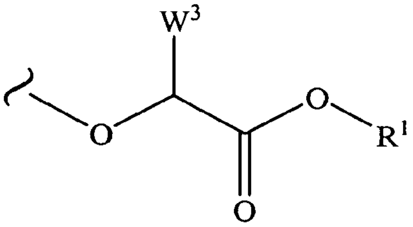

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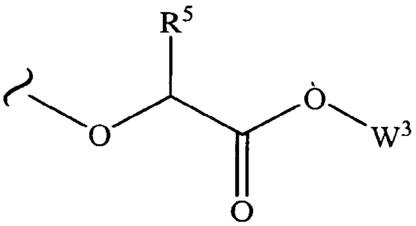

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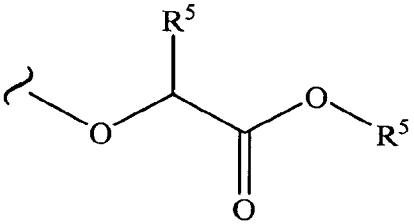

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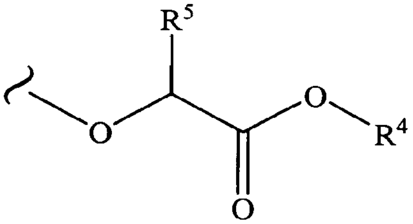

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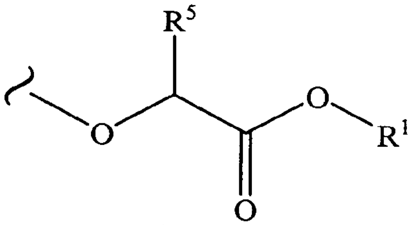

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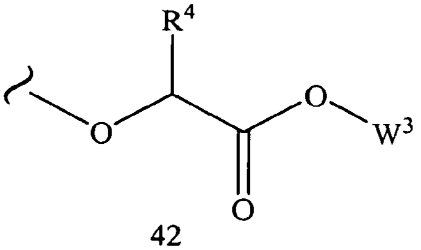
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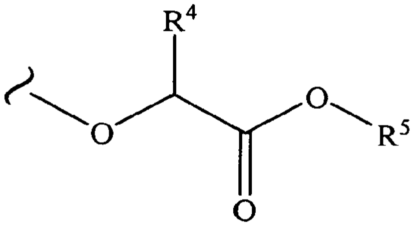
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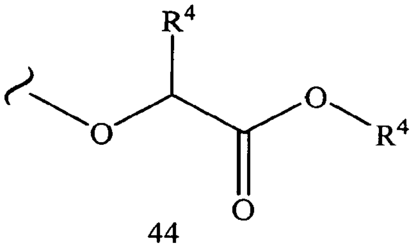
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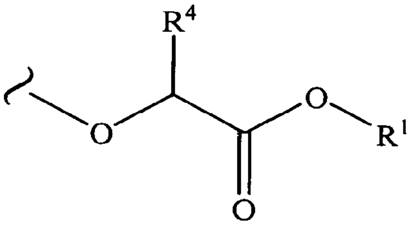
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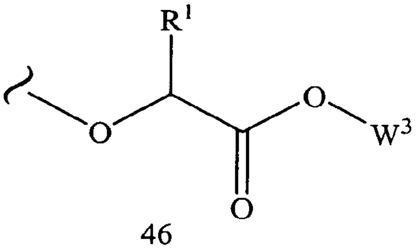
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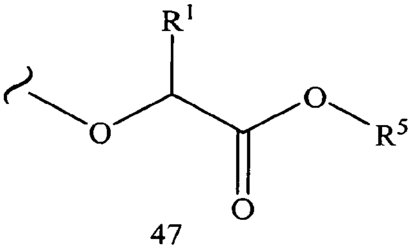
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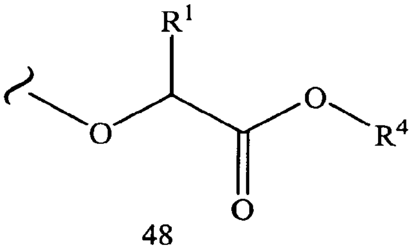
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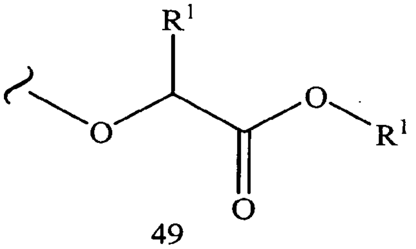
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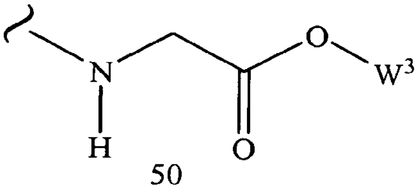
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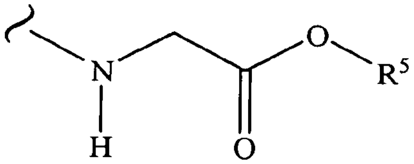
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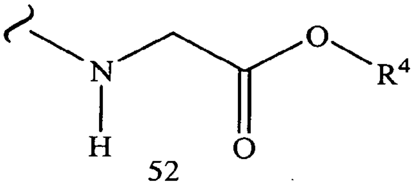
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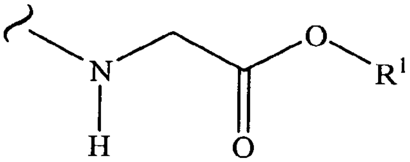
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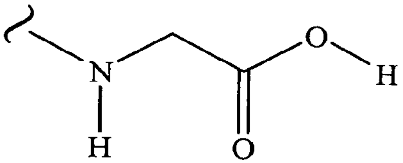
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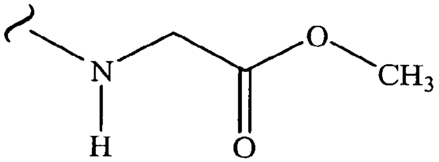
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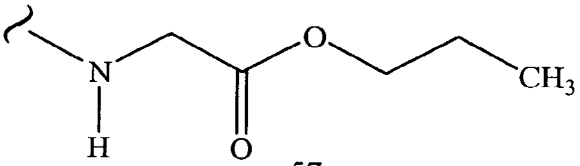
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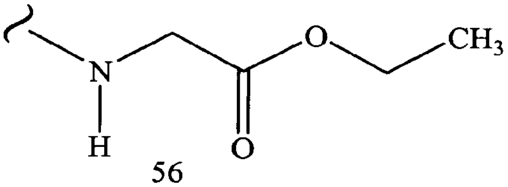
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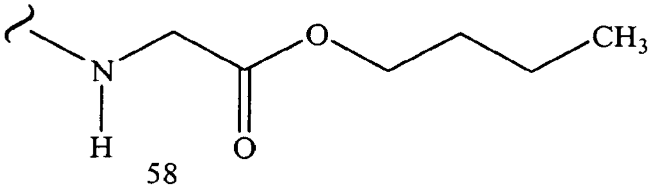

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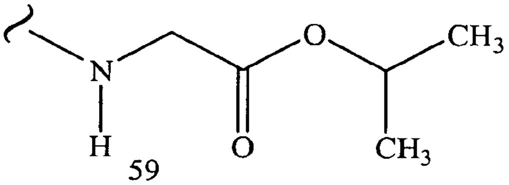

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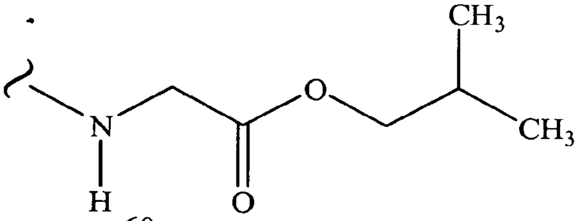

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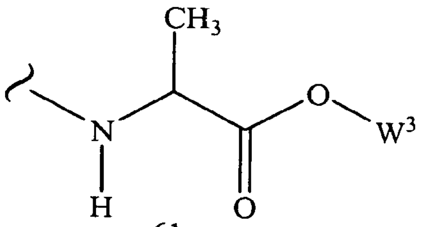
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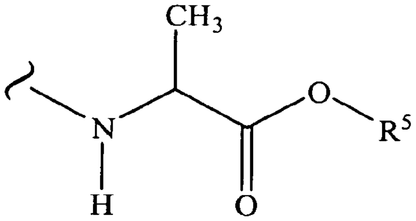
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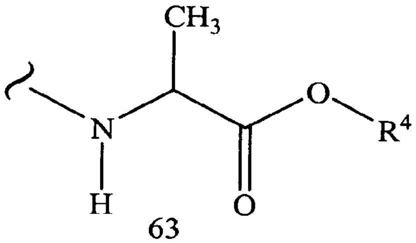
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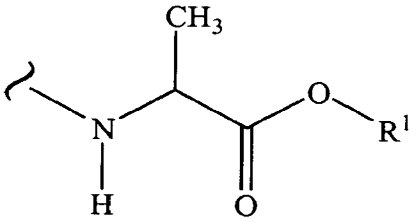
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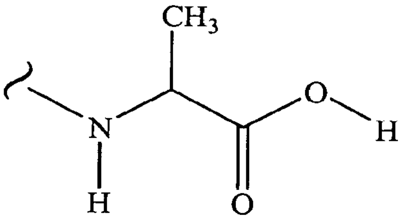
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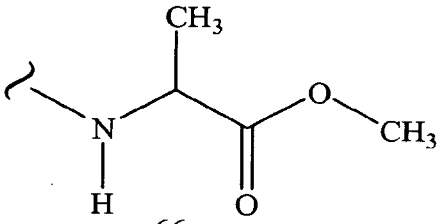
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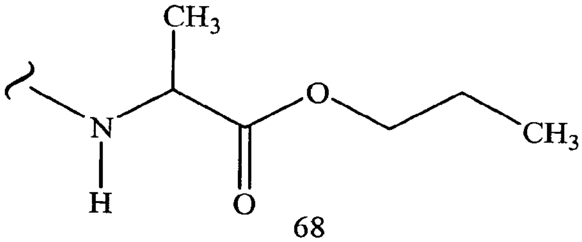
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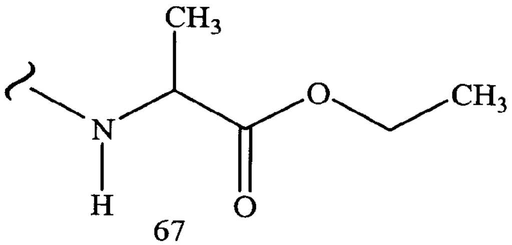
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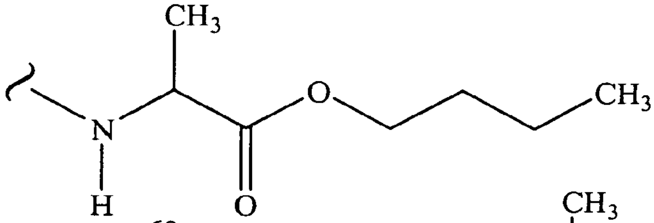
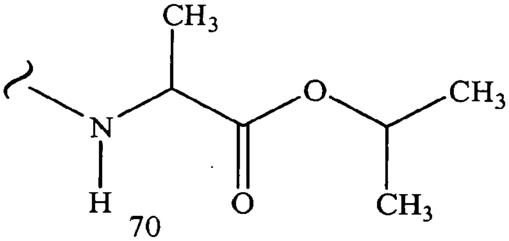
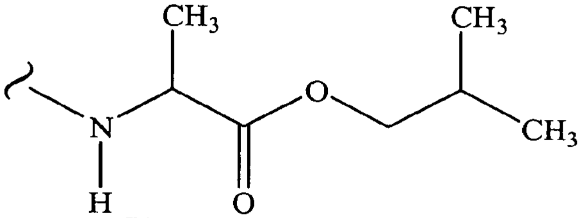

CH3
N
H
O
O
CH3

69


CH3
N
H
O
O
CH3
CH3

70


CH3
CH3
N
H
O
O
CH3

71

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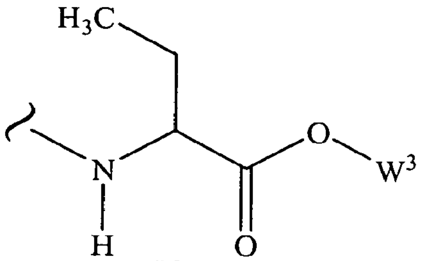
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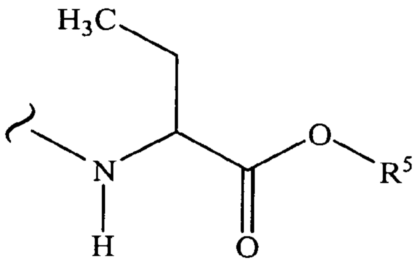
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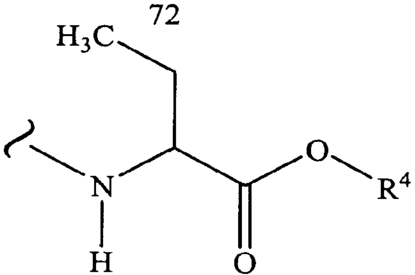
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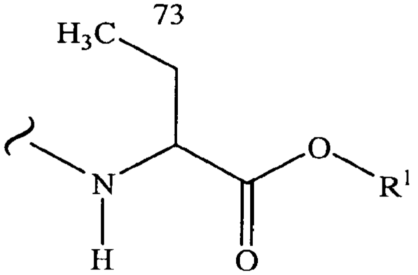
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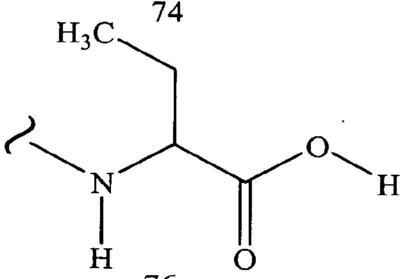
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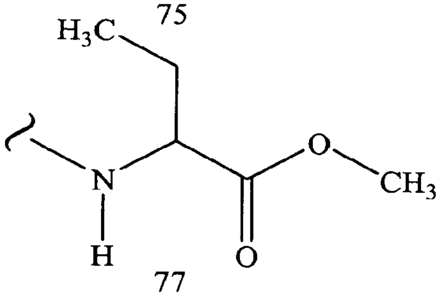
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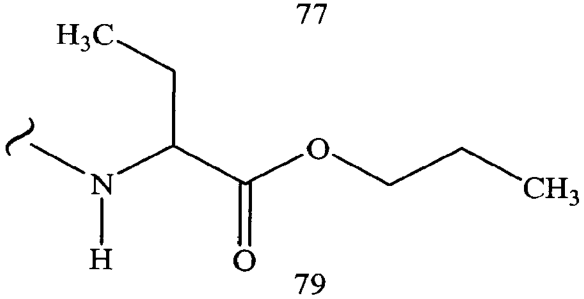
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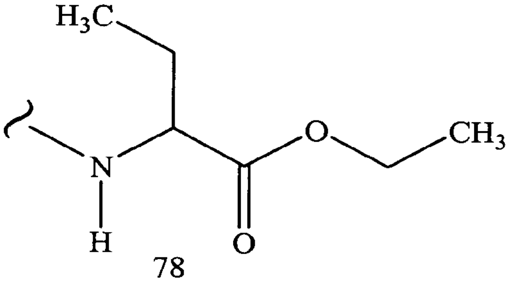
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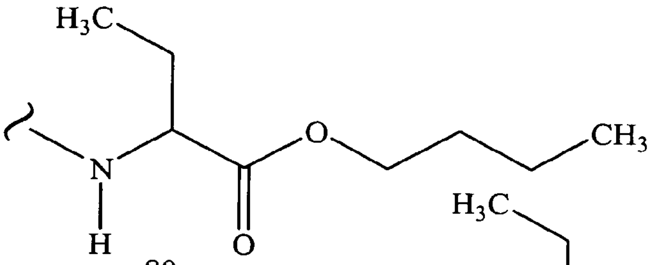

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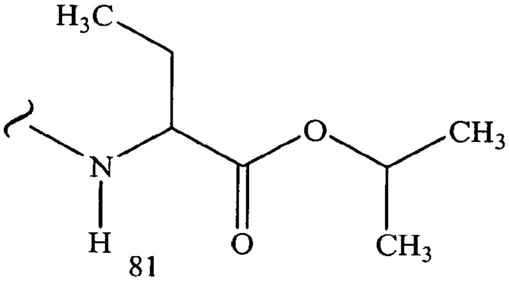

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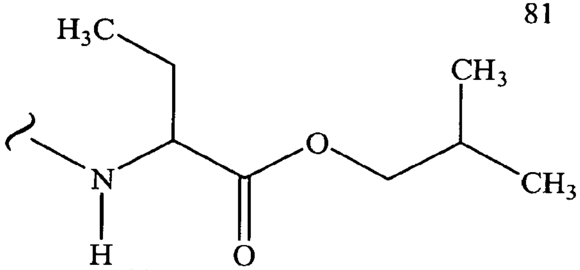

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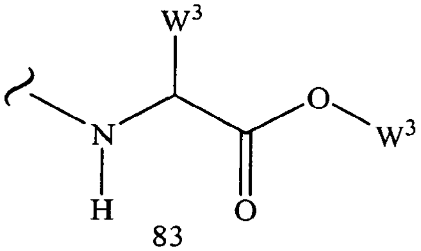

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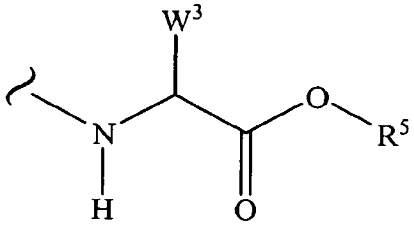

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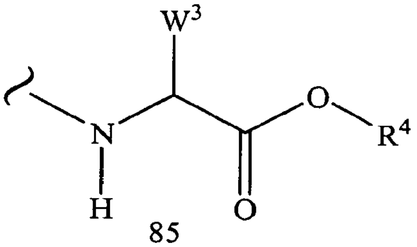

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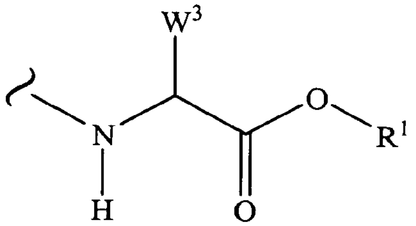

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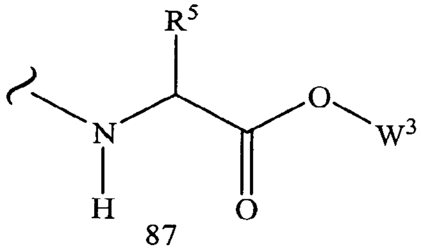

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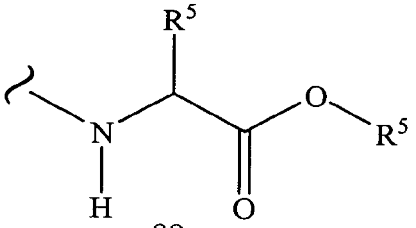

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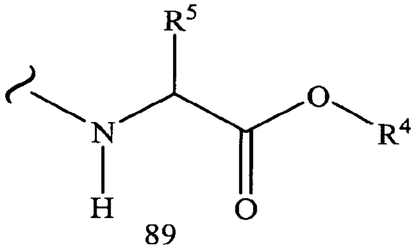

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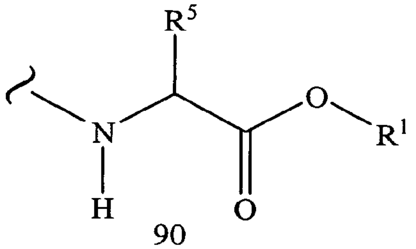

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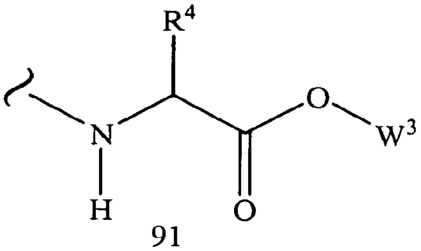

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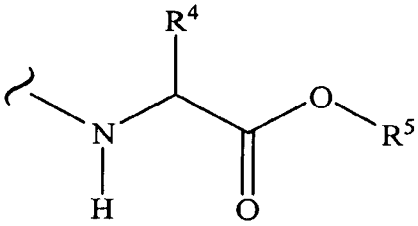

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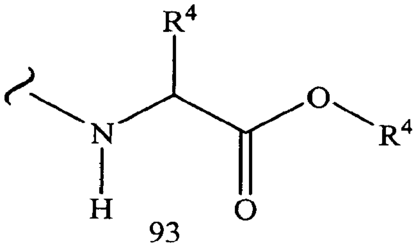

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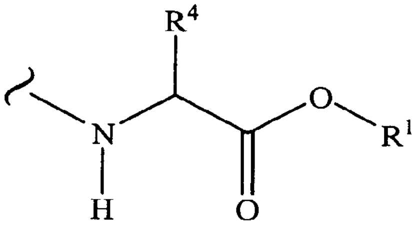

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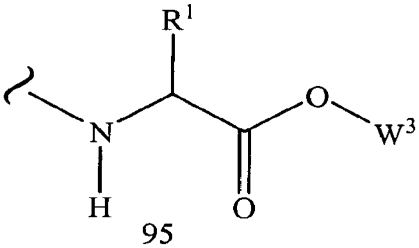

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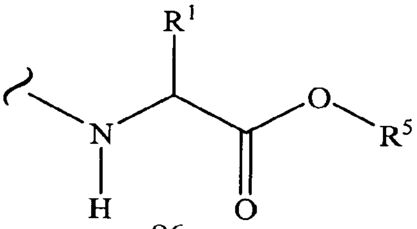

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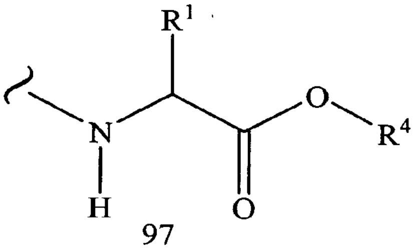

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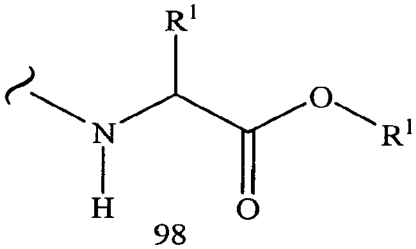

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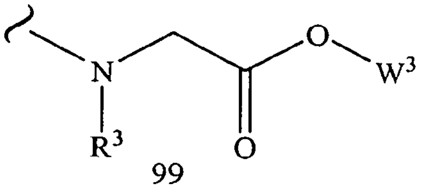

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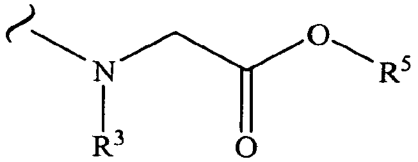

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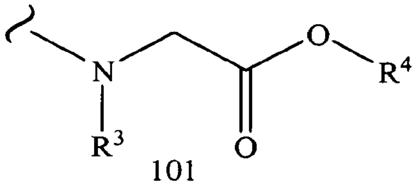

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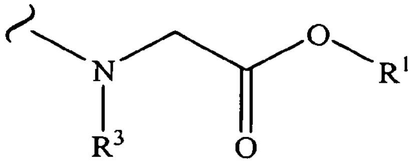

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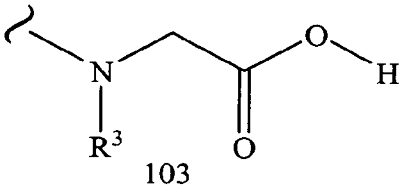

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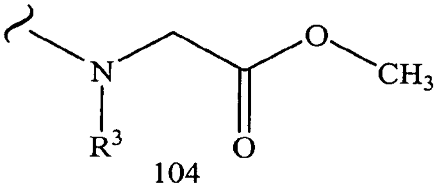

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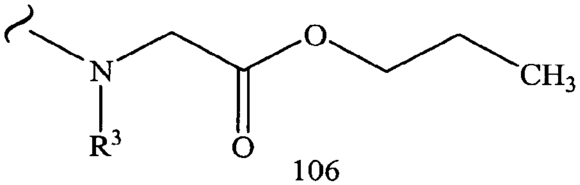

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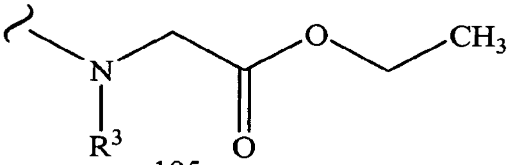

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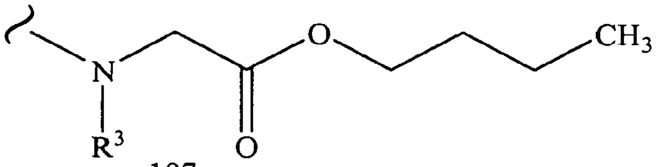

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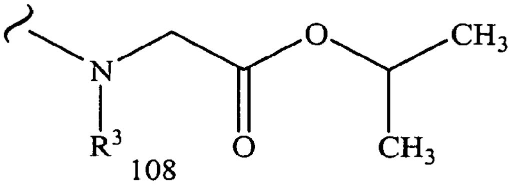

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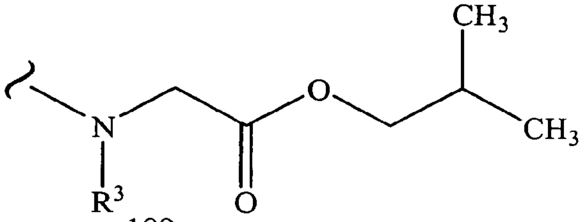

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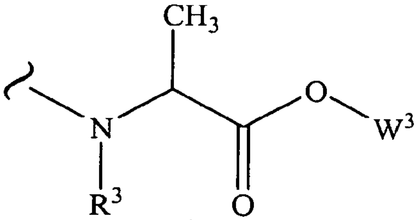
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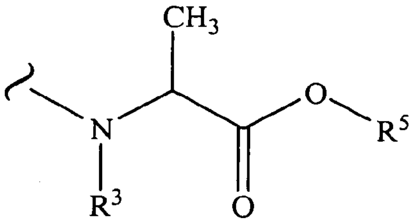
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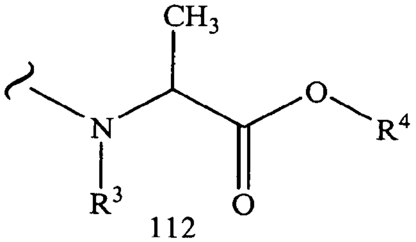
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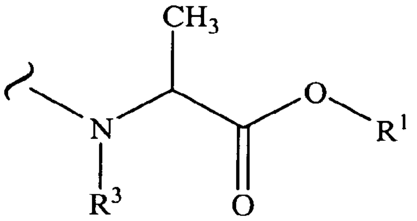
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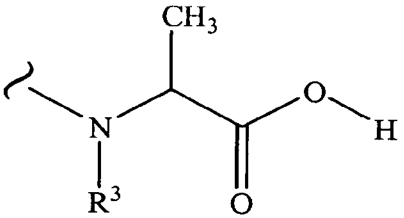
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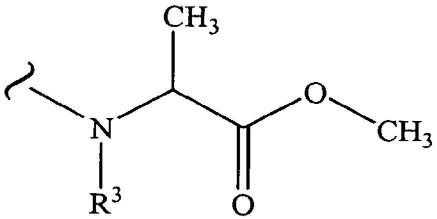
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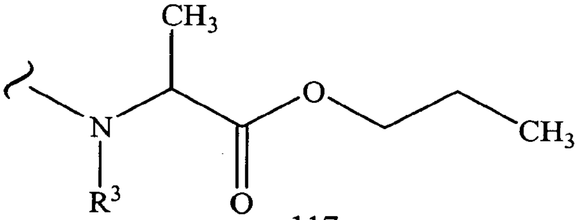
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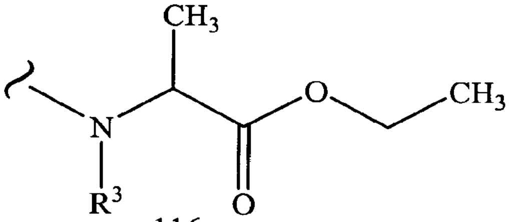
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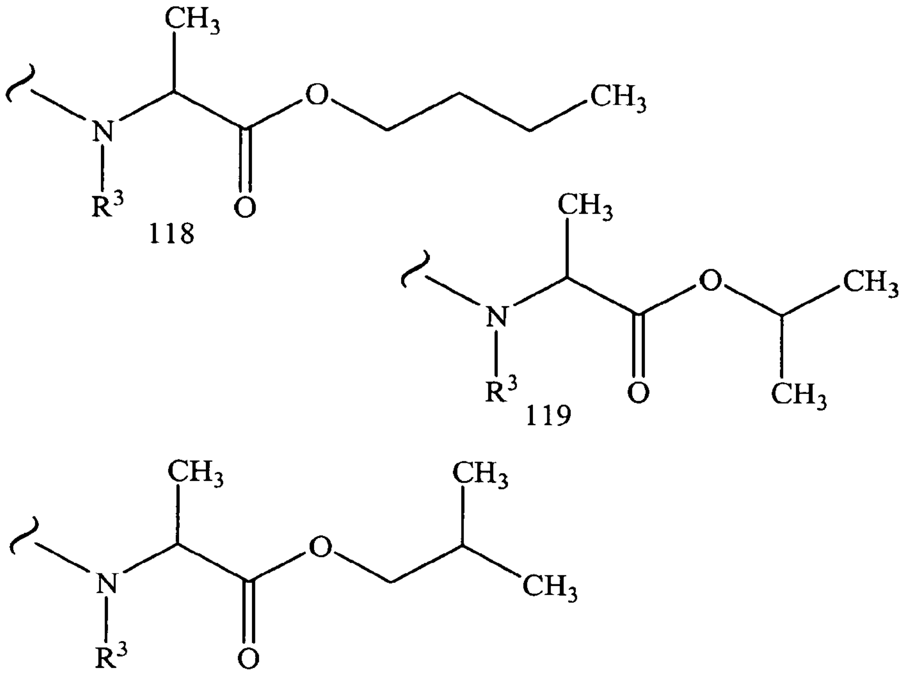
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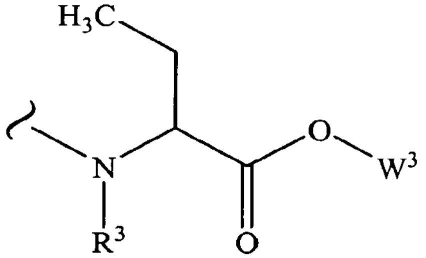
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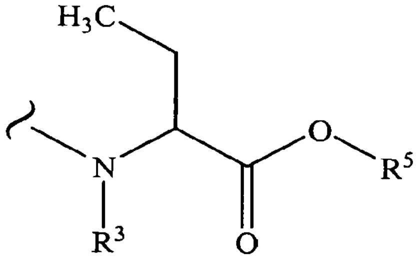
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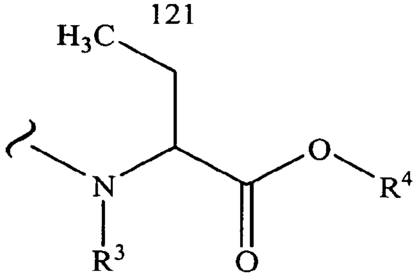
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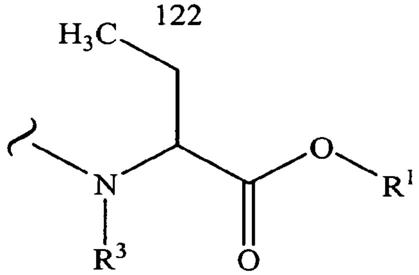
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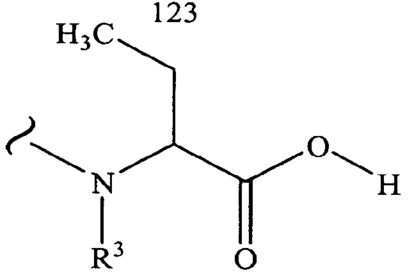
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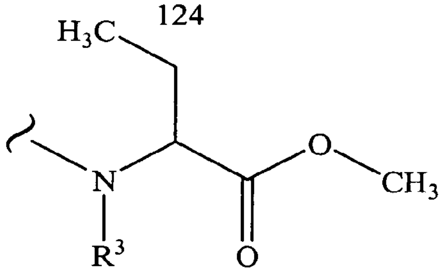
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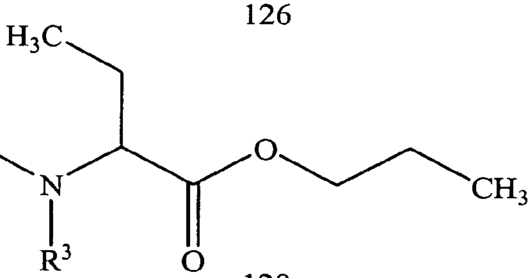
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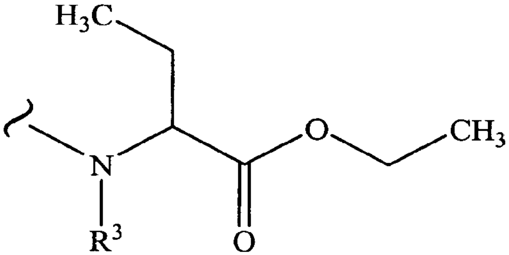
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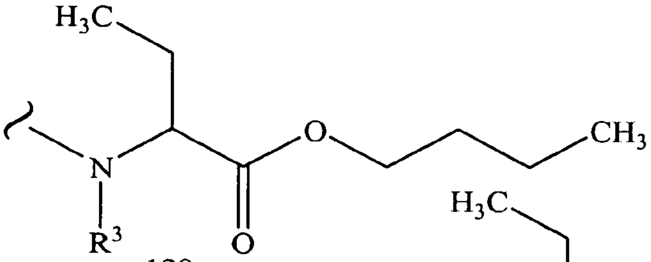
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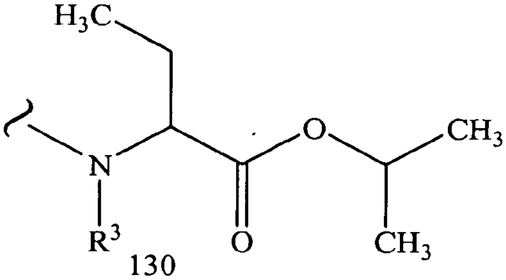
CH3
O
N
R3
O

129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O
CH3
N
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O
CH3

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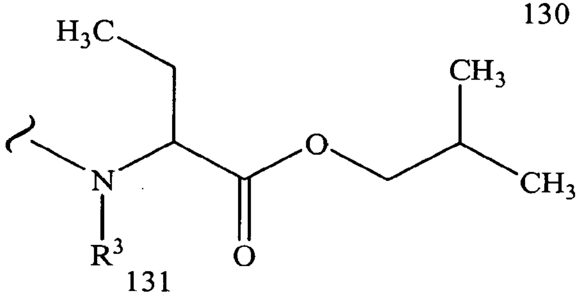
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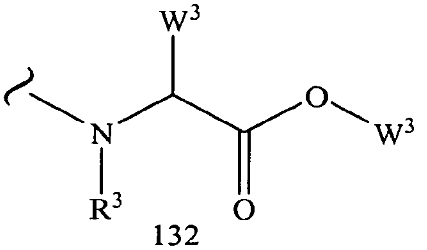
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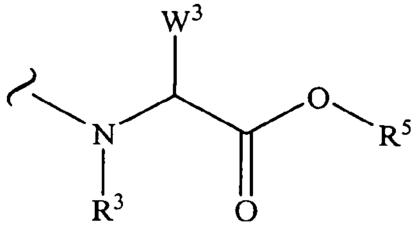
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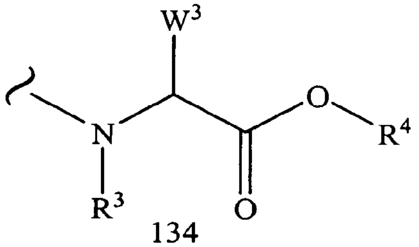
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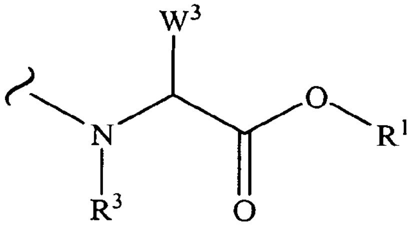
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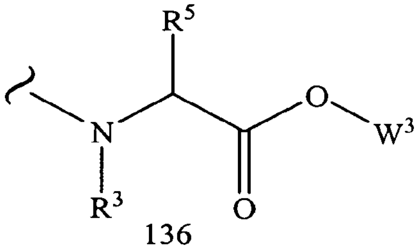
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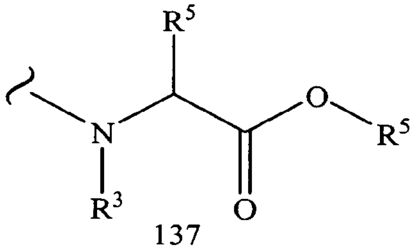
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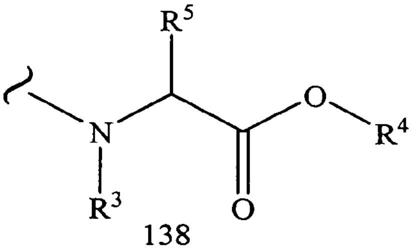
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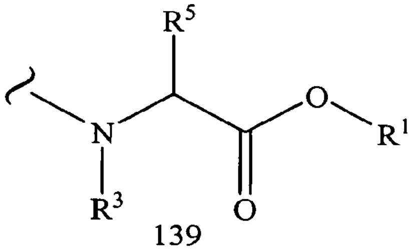
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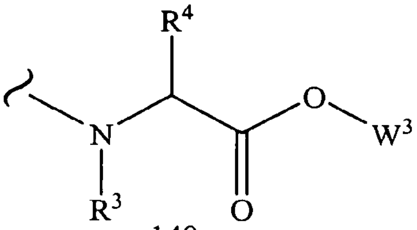
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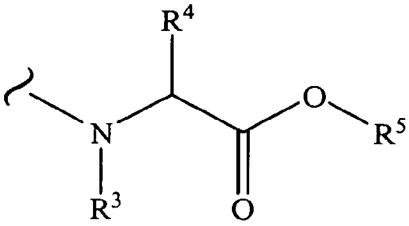
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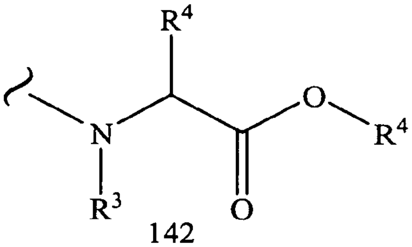
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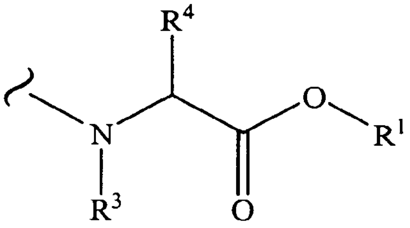
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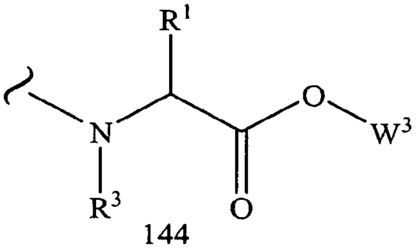
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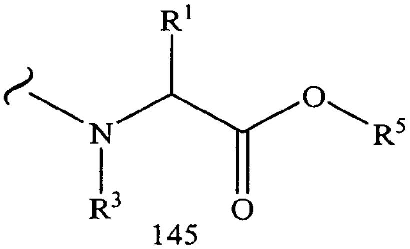
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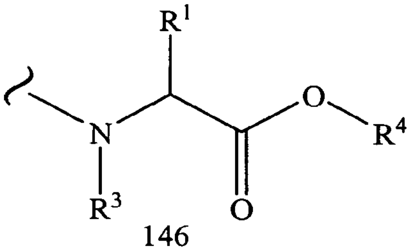
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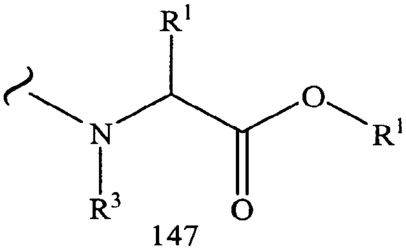
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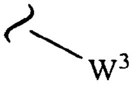

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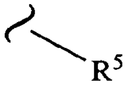

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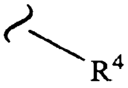

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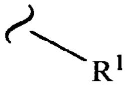

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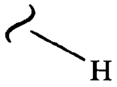

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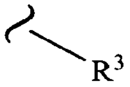

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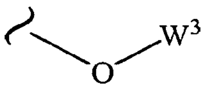

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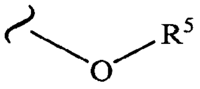

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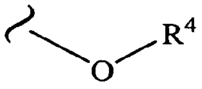

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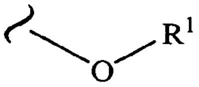

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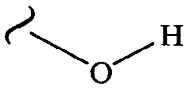

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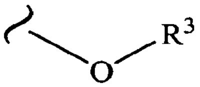

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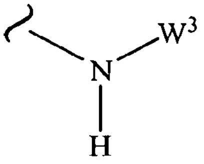

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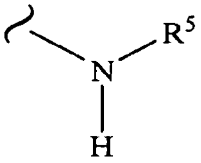

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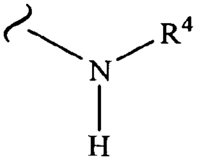

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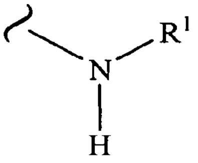

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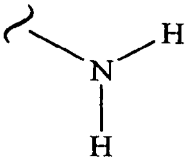

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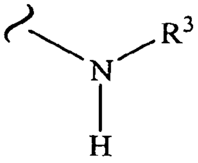

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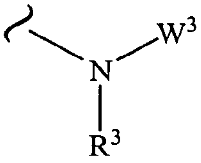

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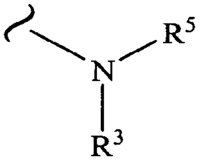

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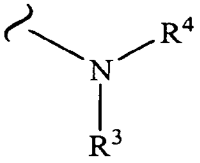

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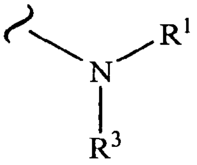

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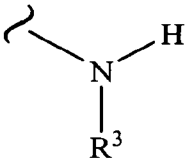

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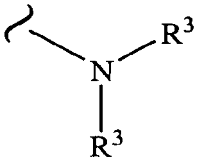

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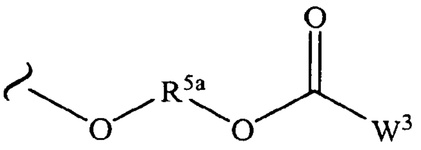

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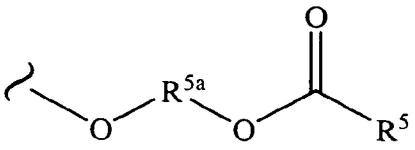

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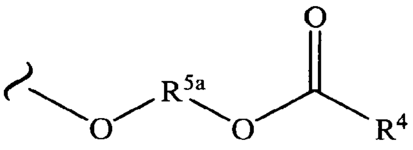

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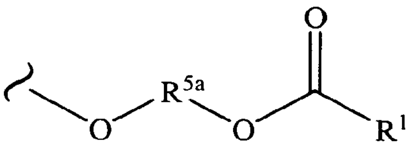

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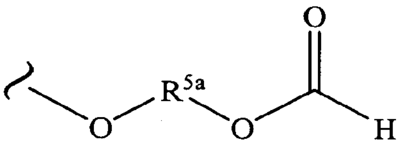

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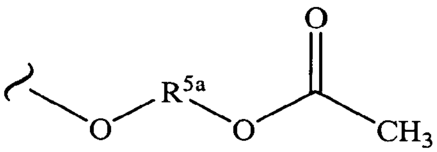

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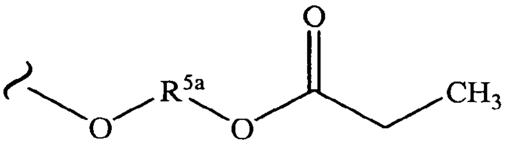

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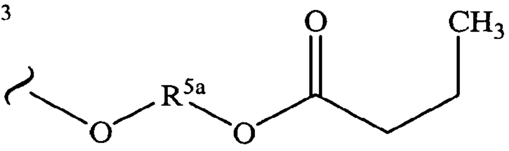

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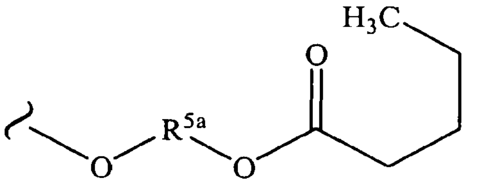

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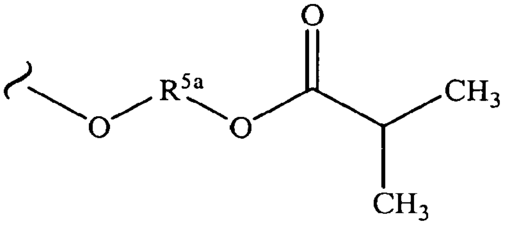

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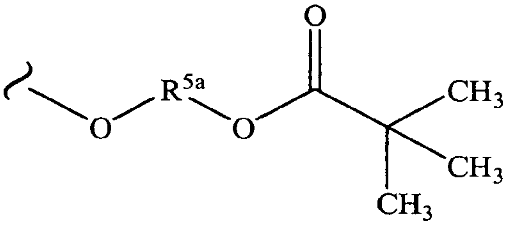

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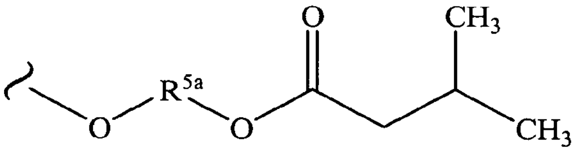

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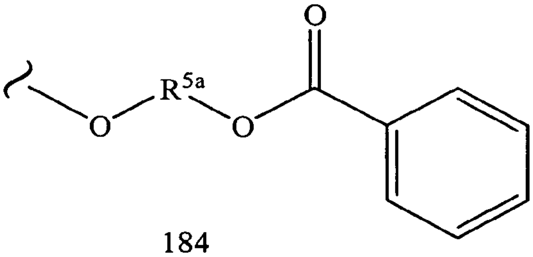

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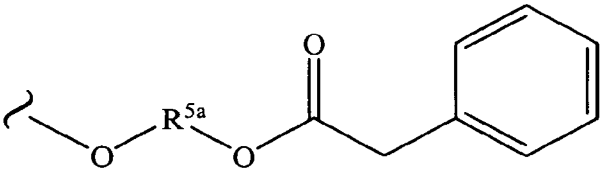

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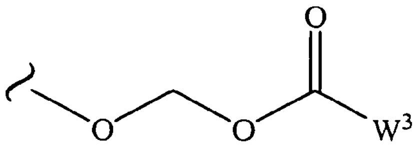

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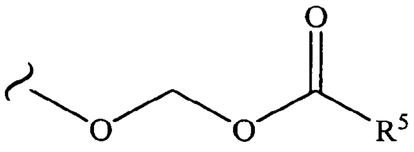

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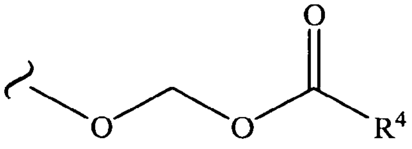

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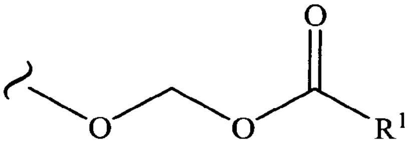

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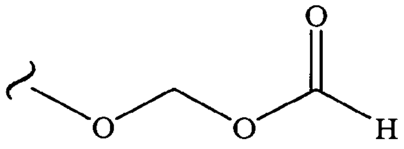

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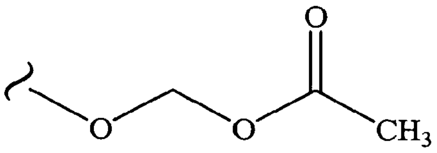

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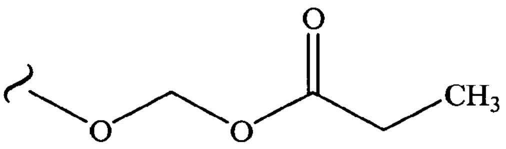

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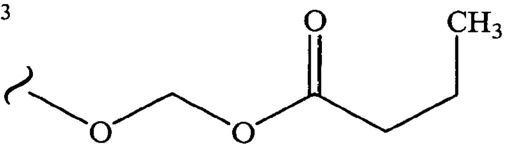

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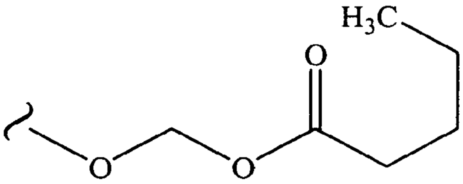

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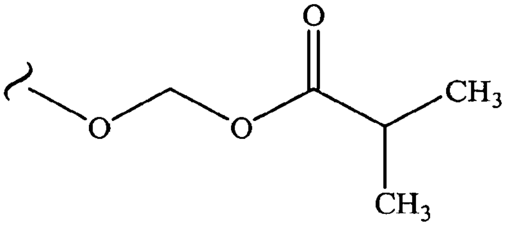

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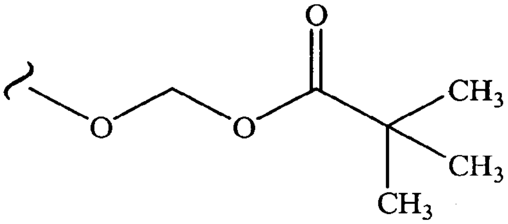

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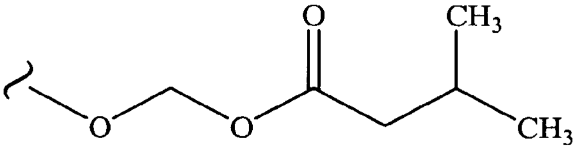

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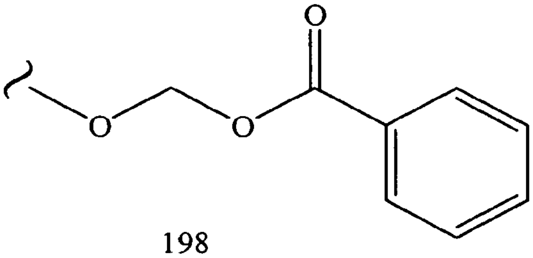

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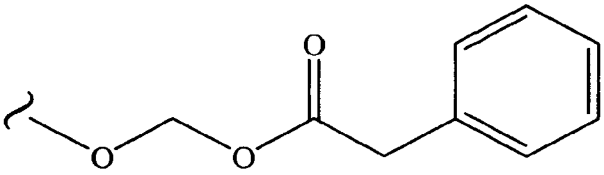

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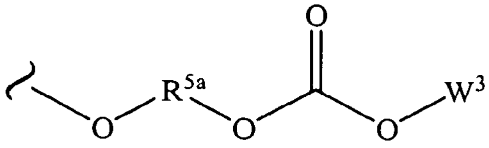

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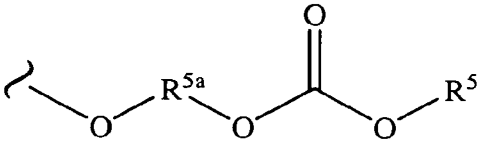

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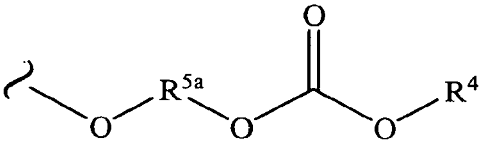

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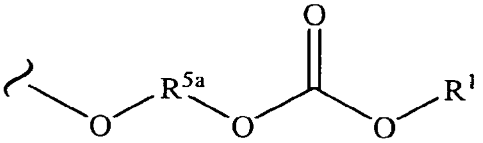

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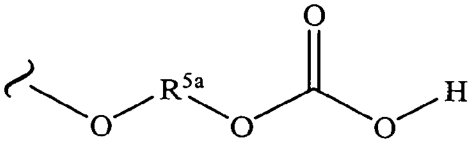

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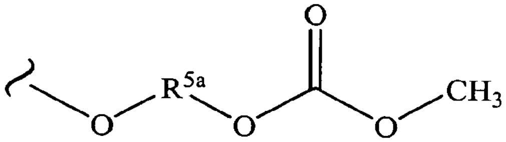
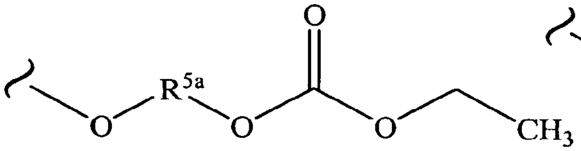
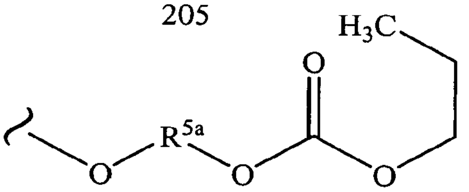

O
R5a
O
O
O
CH3

205


O
R5a
O
O
O
CH3

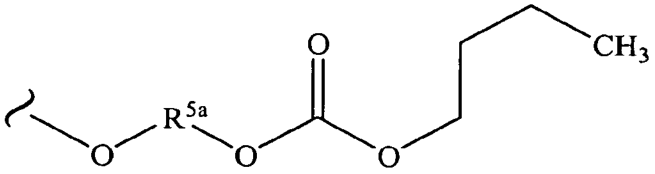
206


H3C
O
R5a
O
O
O

207

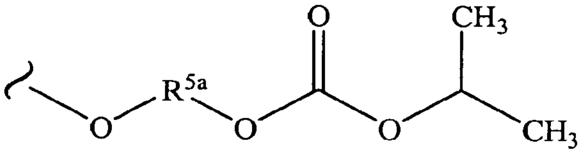
5

Table 20.32



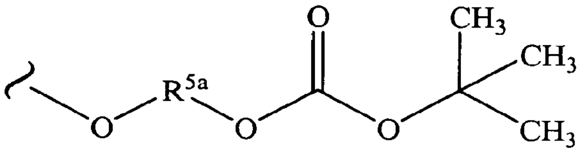
O
CH3
R5a
O
O
O

208



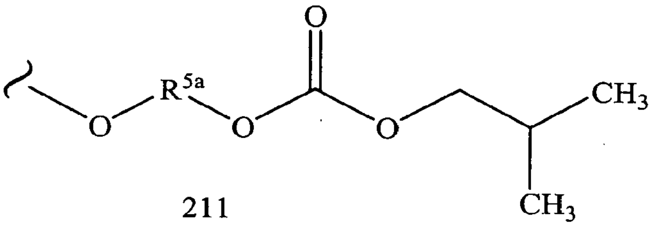
O
CH3
R5a
O
O
O
CH3

209



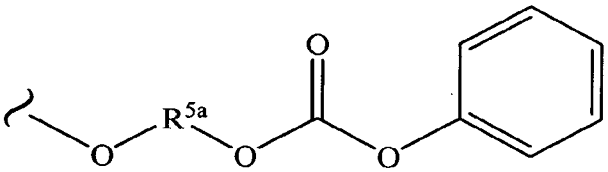
O
CH3
CH3
R5a
O
O
O
CH3

210

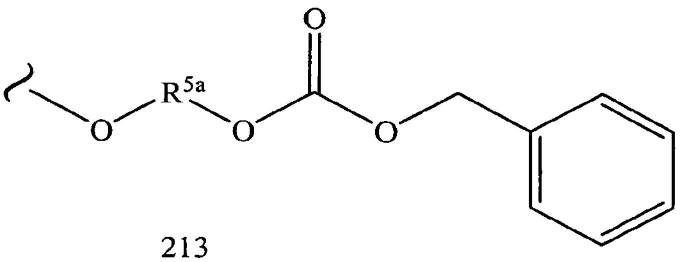


O
R5a
CH3
O
O
O
CH3

211



212



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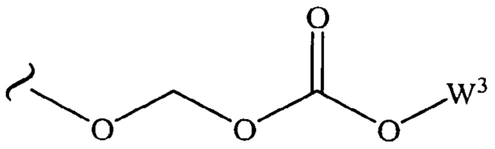

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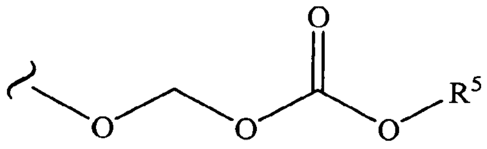

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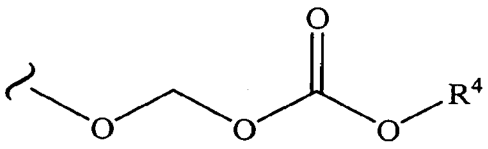

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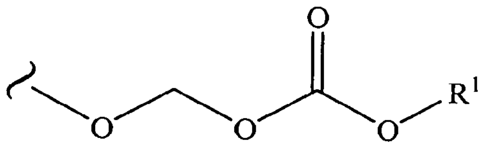

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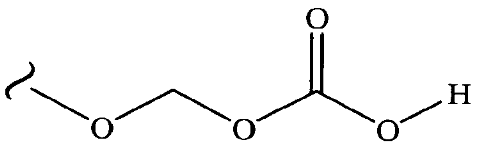

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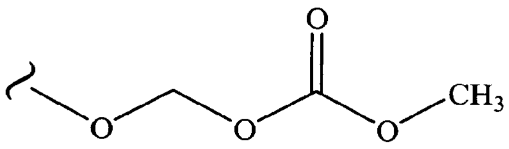

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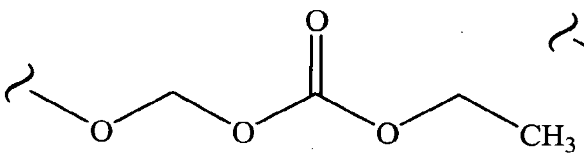

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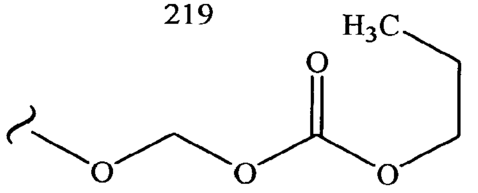

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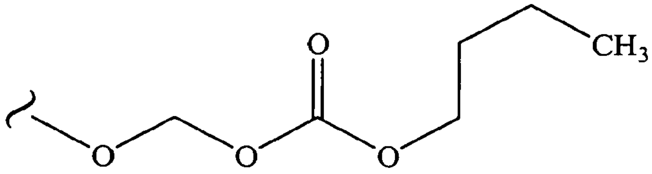

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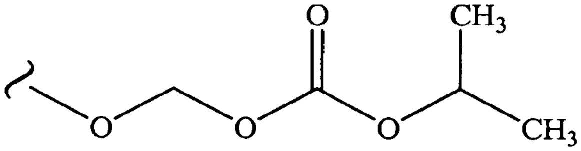

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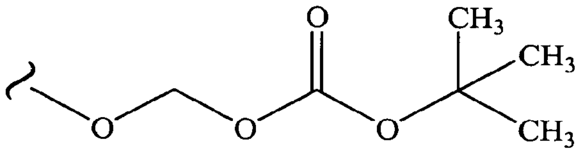

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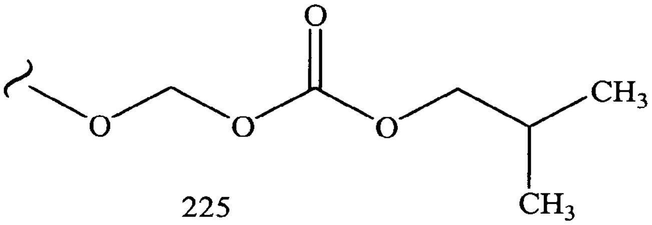

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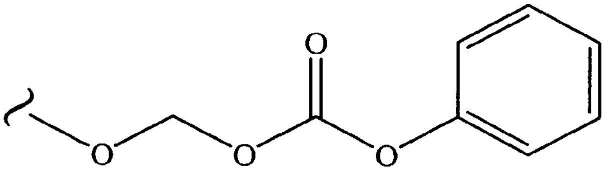

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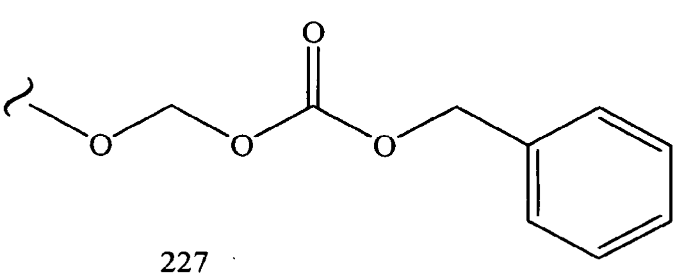

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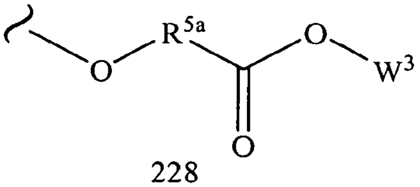
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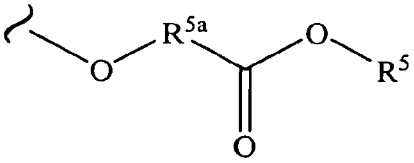
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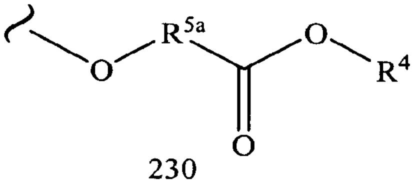
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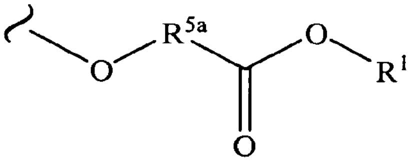
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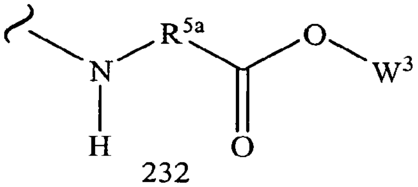
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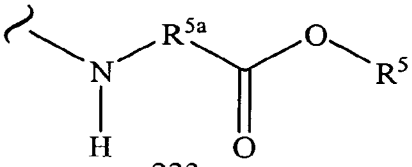
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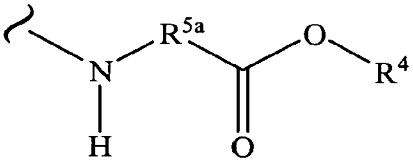
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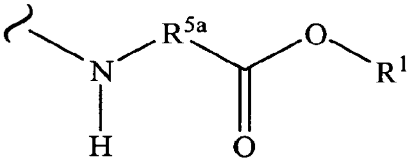
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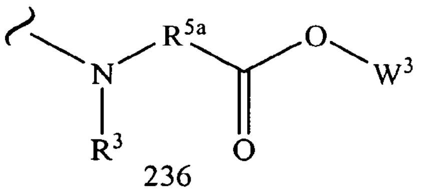
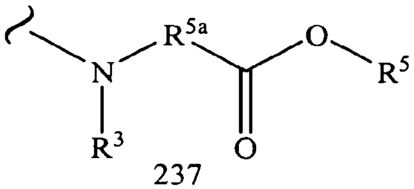
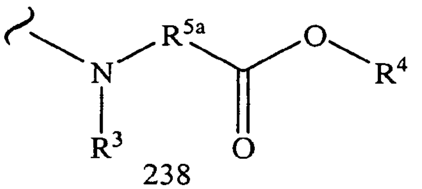

R^5a
O
W^3
N
R^3
O

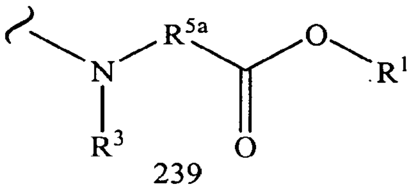
236


R^5a
O
R^5
N
R^3
O

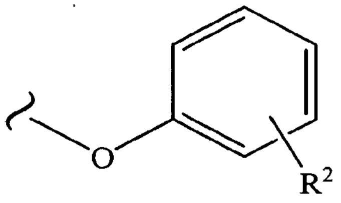
237


R^5a
O
R^4
N
R^3
O

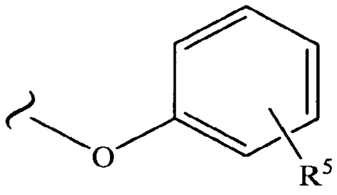
238


R^5a
O
R^1
N
R^3
O

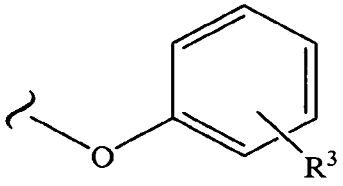
239



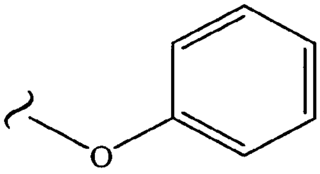
240



241

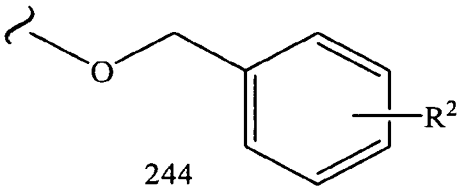


242

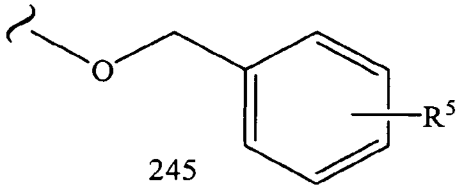


243

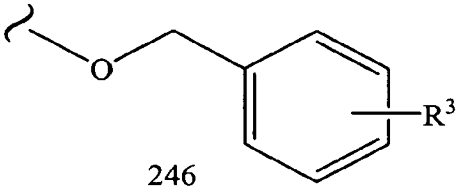
Table 20.37



244



245



246

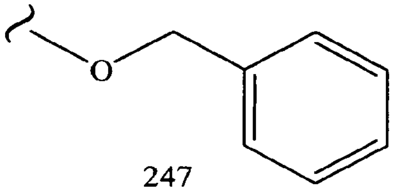


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Table 106

Prodrugs of 1.B

1.B.228.228; 1.B.228.229; 1.B.228.230; 1.B.228.231; 1.B.228.236; 1.B.228.237; 1.B.228.238; 1.B.228.239; 1.B.228.154; 1.B.228.157; 1.B.228.166; 1.B.228.169; 1.B.228.172; 1.B.228.175; 1.B.228.240; 1.B.228.244; 1.B.229.228; 1.B.229.229; 1.B.229.230; 1.B.229.231; 1.B.229.236; 1.B.229.237; 1.B.229.238; 1.B.229.239; 1.B.229.154; 1.B.229.157; 1.B.229.166; 1.B.229.169; 1.B.229.172; 1.B.229.175; 1.B.229.240; 1.B.229.244; 1.B.230.228; 1.B.230.229; 1.B.230.230; 1.B.230.231; 1.B.230.236; 1.B.230.237; 1.B.230.238; 1.B.230.239; 1.B.230.154; 1.B.230.157; 1.B.230.166; 1.B.230.169; 1.B.230.172; 1.B.230.175; 1.B.230.240; 1.B.230.244; 1.B.231.228; 1.B.231.229; 1.B.231.230; 1.B.231.231; 1.B.231.236; 1.B.231.237; 1.B.231.238; 1.B.231.239; 1.B.231.154; 1.B.231.157; 1.B.231.166; 1.B.231.169; 1.B.231.172; 1.B.231.175; 1.B.231.240; 1.B.231.244; 1.B.236.228; 1.B.236.229; 1.B.236.230; 1.B.236.231; 1.B.236.236; 1.B.236.237; 1.B.236.238; 1.B.236.239; 1.B.236.154; 1.B.236.157; 1.B.236.166; 1.B.236.169; 1.B.236.172; 1.B.236.175; 1.B.236.240; 1.B.236.244; 1.B.237.228; 1.B.237.229; 1.B.237.230; 1.B.237.231; 1.B.237.236; 1.B.237.237; 1.B.237.238; 1.B.237.239; 1.B.237.154; 1.B.237.157; 1.B.237.166; 1.B.237.169; 1.B.237.172; 1.B.237.175; 1.B.237.240; 1.B.237.244; 1.B.238.228; 1.B.238.229; 1.B.238.230; 1.B.238.231; 1.B.238.236; 1.B.238.237; 1.B.238.238; 1.B.238.239; 1.B.238.154; 1.B.238.157; 1.B.238.166; 1.B.238.169; 1.B.238.172; 1.B.238.175; 1.B.238.240; 1.B.238.244; 1.B.239.228; 1.B.239.229; 1.B.239.230; 1.B.239.231; 1.B.239.236; 1.B.239.237; 1.B.239.238; 1.B.239.239; 1.B.239.154; 1.B.239.157; 1.B.239.166; 1.B.239.169; 1.B.239.172; 1.B.239.175; 1.B.239.240; 1.B.239.244; 1.B.154.228; 1.B.154.229; 1.B.154.230; 1.B.154.231; 1.B.154.236; 1.B.154.237; 1.B.154.238; 1.B.154.239; 1.B.154.154; 1.B.154.157; 1.B.154.166; 1.B.154.169; 1.B.154.172; 1.B.154.175; 1.B.154.240; 1.B.154.244; 1.B.157.228; 1.B.157.229; 1.B.157.230; 1.B.157.231; 1.B.157.236; 1.B.157.237; 1.B.157.238; 1.B.157.239; 1.B.157.154; 1.B.157.157; 1.B.157.166; 1.B.157.169; 1.B.157.172; 1.B.157.175; 1.B.157.240; 1.B.157.244; 1.B.166.228;

1.B.166.229; 1.B.166.230; 1.B.166.231; 1.B.166.236; 1.B.166.237; 1.B.166.238; 1.B.166.239; 1.B.166.154; 1.B.166.157; 1.B.166.166; 1.B.166.169; 1.B.166.172; 1.B.166.175; 1.B.166.240; 1.B.166.244; 1.B.169.228; 1.B.169.229; 1.B.169.230; 1.B.169.231; 1.B.169.236; 1.B.169.237; 1.B.169.238; 1.B.169.239; 1.B.169.154; 1.B.169.157; 1.B.169.166; 1.B.169.169; 1.B.169.172; 1.B.169.175; 1.B.169.240; 1.B.169.244; 1.B.172.228; 1.B.172.229; 1.B.172.230; 1.B.172.231; 1.B.172.236; 1.B.172.237; 1.B.172.238; 1.B.172.239; 1.B.172.154; 1.B.172.157; 1.B.172.166; 1.B.172.169; 1.B.172.172; 1.B.172.175; 1.B.172.240; 1.B.172.244; 1.B.175.228; 1.B.175.229; 1.B.175.230; 1.B.175.231; 1.B.175.236; 1.B.175.237; 1.B.175.238; 1.B.175.239; 1.B.175.154; 1.B.175.157; 1.B.175.166; 1.B.175.169; 1.B.175.172; 1.B.175.175; 1.B.175.240; 1.B.175.244; 1.B.240.228; 1.B.240.229; 1.B.240.230; 1.B.240.231; 1.B.240.236; 1.B.240.237; 1.B.240.238; 1.B.240.239; 1.B.240.154; 1.B.240.157; 1.B.240.166; 1.B.240.169; 1.B.240.172; 1.B.240.175; 1.B.240.240; 1.B.240.244; 1.B.244.228; 1.B.244.229; 1.B.244.230; 1.B.244.231; 1.B.244.236; 1.B.244.237; 1.B.244.238; 1.B.244.239; 1.B.244.154; 1.B.244.157; 1.B.244.166; 1.B.244.169; 1.B.244.172; 1.B.244.175; 1.B.244.240; 1.B.244.244;

Prodrugs of 1.D

1.D.228.228; 1.D.228.229; 1.D.228.230; 1.D.228.231; 1.D.228.236; 1.D.228.237; 1.D.228.238; 1.D.228.239; 1.D.228.154; 1.D.228.157; 1.D.228.166; 1.D.228.169; 1.D.228.172; 1.D.228.175; 1.D.228.240; 1.D.228.244; 1.D.229.228; 1.D.229.229; 1.D.229.230; 1.D.229.231; 1.D.229.236; 1.D.229.237; 1.D.229.238; 1.D.229.239; 1.D.229.154; 1.D.229.157; 1.D.229.166; 1.D.229.169; 1.D.229.172; 1.D.229.175; 1.D.229.240; 1.D.229.244; 1.D.230.228; 1.D.230.229; 1.D.230.230; 1.D.230.231; 1.D.230.236; 1.D.230.237; 1.D.230.238; 1.D.230.239; 1.D.230.154; 1.D.230.157; 1.D.230.166; 1.D.230.169; 1.D.230.172; 1.D.230.175; 1.D.230.240; 1.D.230.244; 1.D.231.228; 1.D.231.229; 1.D.231.230; 1.D.231.231; 1.D.231.236; 1.D.231.237; 1.D.231.238; 1.D.231.239; 1.D.231.154; 1.D.231.157; 1.D.231.166; 1.D.231.169;

1.D.231.172; 1.D.231.175; 1.D.231.240; 1.D.231.244; 1.D.236.228; 1.D.236.229; 1.D.236.230; 1.D.236.231; 1.D.236.236; 1.D.236.237; 1.D.236.238; 1.D.236.239; 1.D.236.154; 1.D.236.157; 1.D.236.166; 1.D.236.169; 1.D.236.172; 1.D.236.175; 1.D.236.240; 1.D.236.244; 1.D.237.228; 1.D.237.229; 1.D.237.230; 1.D.237.231; 1.D.237.236; 1.D.237.237; 1.D.237.238; 1.D.237.239; 1.D.237.154; 1.D.237.157; 1.D.237.166; 1.D.237.169; 1.D.237.172; 1.D.237.175; 1.D.237.240; 1.D.237.244; 1.D.238.228; 1.D.238.229; 1.D.238.230; 1.D.238.231; 1.D.238.236; 1.D.238.237; 1.D.238.238; 1.D.238.239; 1.D.238.154; 1.D.238.157; 1.D.238.166; 1.D.238.169; 1.D.238.172; 1.D.238.175; 1.D.238.240; 1.D.238.244; 1.D.239.228; 1.D.239.229; 1.D.239.230; 1.D.239.231; 1.D.239.236; 1.D.239.237; 1.D.239.238; 1.D.239.239; 1.D.239.154; 1.D.239.157; 1.D.239.166; 1.D.239.169; 1.D.239.172; 1.D.239.175; 1.D.239.240; 1.D.239.244; 1.D.154.228; 1.D.154.229; 1.D.154.230; 1.D.154.231; 1.D.154.236; 1.D.154.237; 1.D.154.238; 1.D.154.239; 1.D.154.154; 1.D.154.157; 1.D.154.166; 1.D.154.169; 1.D.154.172; 1.D.154.175; 1.D.154.240; 1.D.154.244; 1.D.157.228; 1.D.157.229; 1.D.157.230; 1.D.157.231; 1.D.157.236; 1.D.157.237; 1.D.157.238; 1.D.157.239; 1.D.157.154; 1.D.157.157; 1.D.157.166; 1.D.157.169; 1.D.157.172; 1.D.157.175; 1.D.157.240; 1.D.157.244; 1.D.166.228; 1.D.166.229; 1.D.166.230; 1.D.166.231; 1.D.166.236; 1.D.166.237; 1.D.166.238; 1.D.166.239; 1.D.166.154; 1.D.166.157; 1.D.166.166; 1.D.166.169; 1.D.166.172; 1.D.166.175; 1.D.166.240; 1.D.166.244; 1.D.169.228; 1.D.169.229; 1.D.169.230; 1.D.169.231; 1.D.169.236; 1.D.169.237; 1.D.169.238; 1.D.169.239; 1.D.169.154; 1.D.169.157; 1.D.169.166; 1.D.169.169; 1.D.169.172; 1.D.169.175; 1.D.169.240; 1.D.169.244; 1.D.172.228; 1.D.172.229; 1.D.172.230; 1.D.172.231; 1.D.172.236; 1.D.172.237; 1.D.172.238; 1.D.172.239; 1.D.172.154; 1.D.172.157; 1.D.172.166; 1.D.172.169; 1.D.172.172; 1.D.172.175; 1.D.172.240; 1.D.172.244; 1.D.175.228; 1.D.175.229;

1.D.175.230; 1.D.175.231; 1.D.175.236; 1.D.175.237; 1.D.175.238; 1.D.175.239; 1.D.175.154; 1.D.175.157; 1.D.175.166; 1.D.175.169; 1.D.175.172; 1.D.175.175; 1.D.175.240; 1.D.175.244; 1.D.240.228; 1.D.240.229; 1.D.240.230; 1.D.240.231; 1.D.240.236; 1.D.240.237; 1.D.240.238; 1.D.240.239; 1.D.240.154; 1.D.240.157; 1.D.240.166; 1.D.240.169; 1.D.240.172; 1.D.240.175; 1.D.240.240; 1.D.240.244; 1.D.244.228; 1.D.244.229; 1.D.244.230; 1.D.244.231; 1.D.244.236; 1.D.244.237; 1.D.244.238; 1.D.244.239; 1.D.244.154; 1.D.244.157; 1.D.244.166; 1.D.244.169; 1.D.244.172; 1.D.244.175; 1.D.244.240; 1.D.244.244;

Prodrugs of 1.E

1.E.228.228; 1.E.228.229; 1.E.228.230; 1.E.228.231; 1.E.228.236; 1.E.228.237; 1.E.228.238; 1.E.228.239; 1.E.228.154; 1.E.228.157; 1.E.228.166; 1.E.228.169; 1.E.228.172; 1.E.228.175; 1.E.228.240; 1.E.228.244; 1.E.229.228; 1.E.229.229; 1.E.229.230; 1.E.229.231; 1.E.229.236; 1.E.229.237; 1.E.229.238; 1.E.229.239; 1.E.229.154; 1.E.229.157; 1.E.229.166; 1.E.229.169; 1.E.229.172; 1.E.229.175; 1.E.229.240; 1.E.229.244; 1.E.230.228; 1.E.230.229; 1.E.230.230; 1.E.230.231; 1.E.230.236; 1.E.230.237; 1.E.230.238; 1.E.230.239; 1.E.230.154; 1.E.230.157; 1.E.230.166; 1.E.230.169; 1.E.230.172; 1.E.230.175; 1.E.230.240; 1.E.230.244; 1.E.231.228; 1.E.231.229; 1.E.231.230; 1.E.231.231; 1.E.231.236; 1.E.231.237; 1.E.231.238; 1.E.231.239; 1.E.231.154; 1.E.231.157; 1.E.231.166; 1.E.231.169; 1.E.231.172; 1.E.231.175; 1.E.231.240; 1.E.231.244; 1.E.236.228; 1.E.236.229; 1.E.236.230; 1.E.236.231; 1.E.236.236; 1.E.236.237; 1.E.236.238; 1.E.236.239; 1.E.236.154; 1.E.236.157; 1.E.236.166; 1.E.236.169; 1.E.236.172; 1.E.236.175; 1.E.236.240; 1.E.236.244; 1.E.237.228; 1.E.237.229; 1.E.237.230; 1.E.237.231; 1.E.237.236; 1.E.237.237; 1.E.237.238; 1.E.237.239; 1.E.237.154; 1.E.237.157; 1.E.237.166; 1.E.237.169; 1.E.237.172; 1.E.237.175; 1.E.237.240; 1.E.237.244; 1.E.238.228; 1.E.238.229; 1.E.238.230; 1.E.238.231; 1.E.238.236; 1.E.238.237; 1.E.238.238; 1.E.238.239; 1.E.238.154; 1.E.238.157; 1.E.238.166;

1.E.238.169; 1.E.238.172; 1.E.238.175; 1.E.238.240; 1.E.238.244; 1.E.239.228; 1.E.239.229; 1.E.239.230; 1.E.239.231; 1.E.239.236; 1.E.239.237; 1.E.239.238; 1.E.239.239; 1.E.239.154; 1.E.239.157; 1.E.239.166; 1.E.239.169; 1.E.239.172; 1.E.239.175; 1.E.239.240; 1.E.239.244; 1.E.154.228; 1.E.154.229; 1.E.154.230; 1.E.154.231; 1.E.154.236; 1.E.154.237; 1.E.154.238; 1.E.154.239; 1.E.154.154; 1.E.154.157; 1.E.154.166; 1.E.154.169; 1.E.154.172; 1.E.154.175; 1.E.154.240; 1.E.154.244; 1.E.157.228; 1.E.157.229; 1.E.157.230; 1.E.157.231; 1.E.157.236; 1.E.157.237; 1.E.157.238; 1.E.157.239; 1.E.157.154; 1.E.157.157; 1.E.157.166; 1.E.157.169; 1.E.157.172; 1.E.157.175; 1.E.157.240; 1.E.157.244; 1.E.166.228; 1.E.166.229; 1.E.166.230; 1.E.166.231; 1.E.166.236; 1.E.166.237; 1.E.166.238; 1.E.166.239; 1.E.166.154; 1.E.166.157; 1.E.166.166; 1.E.166.169; 1.E.166.172; 1.E.166.175; 1.E.166.240; 1.E.166.244; 1.E.169.228; 1.E.169.229; 1.E.169.230; 1.E.169.231; 1.E.169.236; 1.E.169.237; 1.E.169.238; 1.E.169.239; 1.E.169.154; 1.E.169.157; 1.E.169.166; 1.E.169.169; 1.E.169.172; 1.E.169.175; 1.E.169.240; 1.E.169.244; 1.E.172.228; 1.E.172.229; 1.E.172.230; 1.E.172.231; 1.E.172.236; 1.E.172.237; 1.E.172.238; 1.E.172.239; 1.E.172.154; 1.E.172.157; 1.E.172.166; 1.E.172.169; 1.E.172.172; 1.E.172.175; 1.E.172.240; 1.E.172.244; 1.E.175.228; 1.E.175.229; 1.E.175.230; 1.E.175.231; 1.E.175.236; 1.E.175.237; 1.E.175.238; 1.E.175.239; 1.E.175.154; 1.E.175.157; 1.E.175.166; 1.E.175.169; 1.E.175.172; 1.E.175.175; 1.E.175.240; 1.E.175.244; 1.E.240.228; 1.E.240.229; 1.E.240.230; 1.E.240.231; 1.E.240.236; 1.E.240.237; 1.E.240.238; 1.E.240.239; 1.E.240.154; 1.E.240.157; 1.E.240.166; 1.E.240.169; 1.E.240.172; 1.E.240.175; 1.E.240.240; 1.E.240.244; 1.E.244.228; 1.E.244.229; 1.E.244.230; 1.E.244.231; 1.E.244.236; 1.E.244.237; 1.E.244.238; 1.E.244.239; 1.E.244.154; 1.E.244.157; 1.E.244.166; 1.E.244.169; 1.E.244.172; 1.E.244.175; 1.E.244.240; 1.E.244.244;

Prodrugs of 1.G

1.G.228.228; 1.G.228.229; 1.G.228.230; 1.G.228.231; 1.G.228.236; 1.G.228.237; 1.G.228.238; 1.G.228.239; 1.G.228.154; 1.G.228.157; 1.G.228.166; 1.G.228.169; 1.G.228.172; 1.G.228.175; 1.G.228.240;

1.G.228.244; 1.G.229.228; 1.G.229.229; 1.G.229.230; 1.G.229.231; 1.G.229.236; 1.G.229.237; 1.G.229.238; 1.G.229.239; 1.G.229.154; 1.G.229.157; 1.G.229.166; 1.G.229.169; 1.G.229.172; 1.G.229.175; 1.G.229.240; 1.G.229.244; 1.G.230.228; 1.G.230.229; 1.G.230.230; 1.G.230.231; 1.G.230.236; 1.G.230.237; 1.G.230.238; 1.G.230.239; 1.G.230.154; 1.G.230.157; 1.G.230.166; 1.G.230.169; 1.G.230.172; 1.G.230.175; 1.G.230.240; 1.G.230.244; 1.G.231.228; 1.G.231.229; 1.G.231.230; 1.G.231.231; 1.G.231.236; 1.G.231.237; 1.G.231.238; 1.G.231.239; 1.G.231.154; 1.G.231.157; 1.G.231.166; 1.G.231.169; 1.G.231.172; 1.G.231.175; 1.G.231.240; 1.G.231.244; 1.G.236.228; 1.G.236.229; 1.G.236.230; 1.G.236.231; 1.G.236.236; 1.G.236.237; 1.G.236.238; 1.G.236.239; 1.G.236.154; 1.G.236.157; 1.G.236.166; 1.G.236.169; 1.G.236.172; 1.G.236.175; 1.G.236.240; 1.G.236.244; 1.G.237.228; 1.G.237.229; 1.G.237.230; 1.G.237.231; 1.G.237.236; 1.G.237.237; 1.G.237.238; 1.G.237.239; 1.G.237.154; 1.G.237.157; 1.G.237.166; 1.G.237.169; 1.G.237.172; 1.G.237.175; 1.G.237.240; 1.G.237.244; 1.G.238.228; 1.G.238.229; 1.G.238.230; 1.G.238.231; 1.G.238.236; 1.G.238.237; 1.G.238.238; 1.G.238.239; 1.G.238.154; 1.G.238.157; 1.G.238.166; 1.G.238.169; 1.G.238.172; 1.G.238.175; 1.G.238.240; 1.G.238.244; 1.G.239.228; 1.G.239.229; 1.G.239.230; 1.G.239.231; 1.G.239.236; 1.G.239.237; 1.G.239.238; 1.G.239.239; 1.G.239.154; 1.G.239.157; 1.G.239.166; 1.G.239.169; 1.G.239.172; 1.G.239.175; 1.G.239.240; 1.G.239.244; 1.G.154.228; 1.G.154.229; 1.G.154.230; 1.G.154.231; 1.G.154.236; 1.G.154.237; 1.G.154.238; 1.G.154.239; 1.G.154.154; 1.G.154.157; 1.G.154.166; 1.G.154.169; 1.G.154.172; 1.G.154.175; 1.G.154.240; 1.G.154.244; 1.G.157.228; 1.G.157.229; 1.G.157.230; 1.G.157.231; 1.G.157.236; 1.G.157.237; 1.G.157.238; 1.G.157.239; 1.G.157.154; 1.G.157.157; 1.G.157.166; 1.G.157.169; 1.G.157.172; 1.G.157.175; 1.G.157.240; 1.G.157.244; 1.G.166.228; 1.G.166.229; 1.G.166.230; 1.G.166.231; 1.G.166.236;

1.G.166.237; 1.G.166.238; 1.G.166.239; 1.G.166.154; 1.G.166.157; 1.G.166.166; 1.G.166.169; 1.G.166.172; 1.G.166.175; 1.G.166.240; 1.G.166.244; 1.G.169.228; 1.G.169.229; 1.G.169.230; 1.G.169.231; 1.G.169.236; 1.G.169.237; 1.G.169.238; 1.G.169.239; 1.G.169.154; 1.G.169.157; 1.G.169.166; 1.G.169.169; 1.G.169.172; 1.G.169.175; 1.G.169.240; 1.G.169.244; 1.G.172.228; 1.G.172.229; 1.G.172.230; 1.G.172.231; 1.G.172.236; 1.G.172.237; 1.G.172.238; 1.G.172.239; 1.G.172.154; 1.G.172.157; 1.G.172.166; 1.G.172.169; 1.G.172.172; 1.G.172.175; 1.G.172.240; 1.G.172.244; 1.G.175.228; 1.G.175.229; 1.G.175.230; 1.G.175.231; 1.G.175.236; 1.G.175.237; 1.G.175.238; 1.G.175.239; 1.G.175.154; 1.G.175.157; 1.G.175.166; 1.G.175.169; 1.G.175.172; 1.G.175.175; 1.G.175.240; 1.G.175.244; 1.G.240.228; 1.G.240.229; 1.G.240.230; 1.G.240.231; 1.G.240.236; 1.G.240.237; 1.G.240.238; 1.G.240.239; 1.G.240.154; 1.G.240.157; 1.G.240.166; 1.G.240.169; 1.G.240.172; 1.G.240.175; 1.G.240.240; 1.G.240.244; 1.G.244.228; 1.G.244.229; 1.G.244.230; 1.G.244.231; 1.G.244.236; 1.G.244.237; 1.G.244.238; 1.G.244.239; 1.G.244.154; 1.G.244.157; 1.G.244.166; 1.G.244.169; 1.G.244.172; 1.G.244.175; 1.G.244.240; 1.G.244.244;

Prodrugs of 1.I

1.I.228.228; 1.I.228.229; 1.I.228.230; 1.I.228.231; 1.I.228.236; 1.I.228.237; 1.I.228.238; 1.I.228.239; 1.I.228.154; 1.I.228.157; 1.I.228.166; 1.I.228.169; 1.I.228.172; 1.I.228.175; 1.I.228.240; 1.I.228.244; 1.I.229.228; 1.I.229.229; 1.I.229.230; 1.I.229.231; 1.I.229.236; 1.I.229.237; 1.I.229.238; 1.I.229.239; 1.I.229.154; 1.I.229.157; 1.I.229.166; 1.I.229.169; 1.I.229.172; 1.I.229.175; 1.I.229.240; 1.I.229.244; 1.I.230.228; 1.I.230.229; 1.I.230.230; 1.I.230.231; 1.I.230.236; 1.I.230.237; 1.I.230.238; 1.I.230.239; 1.I.230.154; 1.I.230.157; 1.I.230.166; 1.I.230.169; 1.I.230.172; 1.I.230.175; 1.I.230.240; 1.I.230.244; 1.I.231.228; 1.I.231.229; 1.I.231.230; 1.I.231.231; 1.I.231.236; 1.I.231.237;

1.I.231.238; 1.I.231.239; 1.I.231.154; 1.I.231.157; 1.I.231.166; 1.I.231.169; 1.I.231.172; 1.I.231.175; 1.I.231.240; 1.I.231.244; 1.I.236.228; 1.I.236.229; 1.I.236.230; 1.I.236.231; 1.I.236.236; 1.I.236.237; 1.I.236.238; 1.I.236.239; 1.I.236.154; 1.I.236.157; 1.I.236.166; 1.I.236.169; 1.I.236.172; 1.I.236.175; 1.I.236.240; 1.I.236.244; 1.I.237.228; 1.I.237.229; 1.I.237.230; 1.I.237.231; 1.I.237.236; 1.I.237.237; 1.I.237.238; 1.I.237.239; 1.I.237.154; 1.I.237.157; 1.I.237.166; 1.I.237.169; 1.I.237.172; 1.I.237.175; 1.I.237.240; 1.I.237.244; 1.I.238.228; 1.I.238.229; 1.I.238.230; 1.I.238.231; 1.I.238.236; 1.I.238.237; 1.I.238.238; 1.I.238.239; 1.I.238.154; 1.I.238.157; 1.I.238.166; 1.I.238.169; 1.I.238.172; 1.I.238.175; 1.I.238.240; 1.I.238.244; 1.I.239.228; 1.I.239.229; 1.I.239.230; 1.I.239.231; 1.I.239.236; 1.I.239.237; 1.I.239.238; 1.I.239.239; 1.I.239.154; 1.I.239.157; 1.I.239.166; 1.I.239.169; 1.I.239.172; 1.I.239.175; 1.I.239.240; 1.I.239.244; 1.I.154.228; 1.I.154.229; 1.I.154.230; 1.I.154.231; 1.I.154.236; 1.I.154.237; 1.I.154.238; 1.I.154.239; 1.I.154.154; 1.I.154.157; 1.I.154.166; 1.I.154.169; 1.I.154.172; 1.I.154.175; 1.I.154.240; 1.I.154.244; 1.I.157.228; 1.I.157.229; 1.I.157.230; 1.I.157.231; 1.I.157.236; 1.I.157.237; 1.I.157.238; 1.I.157.239; 1.I.157.154; 1.I.157.157; 1.I.157.166; 1.I.157.169; 1.I.157.172; 1.I.157.175; 1.I.157.240; 1.I.157.244; 1.I.166.228; 1.I.166.229; 1.I.166.230; 1.I.166.231; 1.I.166.236; 1.I.166.237; 1.I.166.238; 1.I.166.239; 1.I.166.154; 1.I.166.157; 1.I.166.166; 1.I.166.169; 1.I.166.172; 1.I.166.175; 1.I.166.240; 1.I.166.244; 1.I.169.228; 1.I.169.229; 1.I.169.230; 1.I.169.231; 1.I.169.236; 1.I.169.237; 1.I.169.238; 1.I.169.239; 1.I.169.154; 1.I.169.157; 1.I.169.166; 1.I.169.169; 1.I.169.172; 1.I.169.175; 1.I.169.240; 1.I.169.244; 1.I.172.228; 1.I.172.229; 1.I.172.230; 1.I.172.231; 1.I.172.236; 1.I.172.237; 1.I.172.238; 1.I.172.239; 1.I.172.154; 1.I.172.157; 1.I.172.166; 1.I.172.169; 1.I.172.172; 1.I.172.175; 1.I.172.240; 1.I.172.244; 1.I.175.228; 1.I.175.229; 1.I.175.230; 1.I.175.231; 1.I.175.236; 1.I.175.237; 1.I.175.238; 1.I.175.239; 1.I.175.154; 1.I.175.157; 1.I.175.166; 1.I.175.169; 1.I.175.172; 1.I.175.175; 1.I.175.240; 1.I.175.244; 1.I.240.228; 1.I.240.229; 1.I.240.230; 1.I.240.231; 1.I.240.236; 1.I.240.237; 1.I.240.238; 1.I.240.239; 1.I.240.154; 1.I.240.157;

1.I.240.166; 1.I.240.169; 1.I.240.172; 1.I.240.175; 1.I.240.240; 1.I.240.244; 1.I.244.228; 1.I.244.229; 1.I.244.230; 1.I.244.231; 1.I.244.236; 1.I.244.237; 1.I.244.238; 1.I.244.239; 1.I.244.154; 1.I.244.157; 1.I.244.166; 1.I.244.169; 1.I.244.172; 1.I.244.175; 1.I.244.240; 1.I.244.244;

Prodrugs of 1.J

1.J.228.228; 1.J.228.229; 1.J.228.230; 1.J.228.231; 1.J.228.236; 1.J.228.237; 1.J.228.238; 1.J.228.239; 1.J.228.154; 1.J.228.157; 1.J.228.166; 1.J.228.169; 1.J.228.172; 1.J.228.175; 1.J.228.240; 1.J.228.244; 1.J.229.228; 1.J.229.229; 1.J.229.230; 1.J.229.231; 1.J.229.236; 1.J.229.237; 1.J.229.238; 1.J.229.239; 1.J.229.154; 1.J.229.157; 1.J.229.166; 1.J.229.169; 1.J.229.172; 1.J.229.175; 1.J.229.240; 1.J.229.244; 1.J.230.228; 1.J.230.229; 1.J.230.230; 1.J.230.231; 1.J.230.236; 1.J.230.237; 1.J.230.238; 1.J.230.239; 1.J.230.154; 1.J.230.157; 1.J.230.166; 1.J.230.169; 1.J.230.172; 1.J.230.175; 1.J.230.240; 1.J.230.244; 1.J.231.228; 1.J.231.229; 1.J.231.230; 1.J.231.231; 1.J.231.236; 1.J.231.237; 1.J.231.238; 1.J.231.239; 1.J.231.154; 1.J.231.157; 1.J.231.166; 1.J.231.169; 1.J.231.172; 1.J.231.175; 1.J.231.240; 1.J.231.244; 1.J.236.228; 1.J.236.229; 1.J.236.230; 1.J.236.231; 1.J.236.236; 1.J.236.237; 1.J.236.238; 1.J.236.239; 1.J.236.154; 1.J.236.157; 1.J.236.166; 1.J.236.169; 1.J.236.172; 1.J.236.175; 1.J.236.240; 1.J.236.244; 1.J.237.228; 1.J.237.229; 1.J.237.230; 1.J.237.231; 1.J.237.236; 1.J.237.237; 1.J.237.238; 1.J.237.239; 1.J.237.154; 1.J.237.157; 1.J.237.166; 1.J.237.169; 1.J.237.172; 1.J.237.175; 1.J.237.240; 1.J.237.244; 1.J.238.228; 1.J.238.229; 1.J.238.230; 1.J.238.231; 1.J.238.236; 1.J.238.237; 1.J.238.238; 1.J.238.239; 1.J.238.154; 1.J.238.157; 1.J.238.166; 1.J.238.169; 1.J.238.172; 1.J.238.175; 1.J.238.240; 1.J.238.244; 1.J.239.228; 1.J.239.229; 1.J.239.230; 1.J.239.231; 1.J.239.236; 1.J.239.237; 1.J.239.238; 1.J.239.239; 1.J.239.154; 1.J.239.157; 1.J.239.166; 1.J.239.169; 1.J.239.172; 1.J.239.175; 1.J.239.240; 1.J.239.244; 1.J.154.228; 1.J.154.229; 1.J.154.230; 1.J.154.231; 1.J.154.236; 1.J.154.237; 1.J.154.238; 1.J.154.239; 1.J.154.154; 1.J.154.157; 1.J.154.166; 1.J.154.169; 1.J.154.172; 1.J.154.175; 1.J.154.240; 1.J.154.244;

1.J.157.228; 1.J.157.229; 1.J.157.230; 1.J.157.231; 1.J.157.236; 1.J.157.237; 1.J.157.238; 1.J.157.239; 1.J.157.154; 1.J.157.157; 1.J.157.166; 1.J.157.169; 1.J.157.172; 1.J.157.175; 1.J.157.240; 1.J.157.244; 1.J.166.228; 1.J.166.229; 1.J.166.230; 1.J.166.231; 1.J.166.236; 1.J.166.237; 1.J.166.238; 1.J.166.239; 1.J.166.154; 1.J.166.157; 1.J.166.166; 1.J.166.169; 1.J.166.172; 1.J.166.175; 1.J.166.240; 1.J.166.244; 1.J.169.228; 1.J.169.229; 1.J.169.230; 1.J.169.231; 1.J.169.236; 1.J.169.237; 1.J.169.238; 1.J.169.239; 1.J.169.154; 1.J.169.157; 1.J.169.166; 1.J.169.169; 1.J.169.172; 1.J.169.175; 1.J.169.240; 1.J.169.244; 1.J.172.228; 1.J.172.229; 1.J.172.230; 1.J.172.231; 1.J.172.236; 1.J.172.237; 1.J.172.238; 1.J.172.239; 1.J.172.154; 1.J.172.157; 1.J.172.166; 1.J.172.169; 1.J.172.172; 1.J.172.175; 1.J.172.240; 1.J.172.244; 1.J.175.228; 1.J.175.229; 1.J.175.230; 1.J.175.231; 1.J.175.236; 1.J.175.237; 1.J.175.238; 1.J.175.239; 1.J.175.154; 1.J.175.157; 1.J.175.166; 1.J.175.169; 1.J.175.172; 1.J.175.175; 1.J.175.240; 1.J.175.244; 1.J.240.228; 1.J.240.229; 1.J.240.230; 1.J.240.231; 1.J.240.236; 1.J.240.237; 1.J.240.238; 1.J.240.239; 1.J.240.154; 1.J.240.157; 1.J.240.166; 1.J.240.169; 1.J.240.172; 1.J.240.175; 1.J.240.240; 1.J.240.244; 1.J.244.228; 1.J.244.229; 1.J.244.230; 1.J.244.231; 1.J.244.236; 1.J.244.237; 1.J.244.238; 1.J.244.239; 1.J.244.154; 1.J.244.157; 1.J.244.166; 1.J.244.169; 1.J.244.172; 1.J.244.175; 1.J.244.240; 1.J.244.244;

Prodrugs of 1.L

1.L.228.228; 1.L.228.229; 1.L.228.230; 1.L.228.231; 1.L.228.236; 1.L.228.237; 1.L.228.238; 1.L.228.239; 1.L.228.154; 1.L.228.157; 1.L.228.166; 1.L.228.169; 1.L.228.172; 1.L.228.175; 1.L.228.240; 1.L.228.244; 1.L.229.228; 1.L.229.229; 1.L.229.230; 1.L.229.231; 1.L.229.236; 1.L.229.237; 1.L.229.238; 1.L.229.239; 1.L.229.154; 1.L.229.157; 1.L.229.166; 1.L.229.169; 1.L.229.172; 1.L.229.175; 1.L.229.240; 1.L.229.244; 1.L.230.228; 1.L.230.229; 1.L.230.230; 1.L.230.231; 1.L.230.236; 1.L.230.237; 1.L.230.238; 1.L.230.239; 1.L.230.154; 1.L.230.157; 1.L.230.166; 1.L.230.169; 1.L.230.172; 1.L.230.175; 1.L.230.240; 1.L.230.244; 1.L.231.228; 1.L.231.229; 1.L.231.230; 1.L.231.231; 1.L.231.236;

1.L.231.237; 1.L.231.238; 1.L.231.239; 1.L.231.154; 1.L.231.157; 1.L.231.166; 1.L.231.169; 1.L.231.172; 1.L.231.175; 1.L.231.240; 1.L.231.244; 1.L.236.228; 1.L.236.229; 1.L.236.230; 1.L.236.231; 1.L.236.236; 1.L.236.237; 1.L.236.238; 1.L.236.239; 1.L.236.154; 1.L.236.157; 1.L.236.166; 1.L.236.169; 1.L.236.172; 1.L.236.175; 1.L.236.240; 1.L.236.244; 1.L.237.228; 1.L.237.229; 1.L.237.230; 1.L.237.231; 1.L.237.236; 1.L.237.237; 1.L.237.238; 1.L.237.239; 1.L.237.154; 1.L.237.157; 1.L.237.166; 1.L.237.169; 1.L.237.172; 1.L.237.175; 1.L.237.240; 1.L.237.244; 1.L.238.228; 1.L.238.229; 1.L.238.230; 1.L.238.231; 1.L.238.236; 1.L.238.237; 1.L.238.238; 1.L.238.239; 1.L.238.154; 1.L.238.157; 1.L.238.166; 1.L.238.169; 1.L.238.172; 1.L.238.175; 1.L.238.240; 1.L.238.244; 1.L.239.228; 1.L.239.229; 1.L.239.230; 1.L.239.231; 1.L.239.236; 1.L.239.237; 1.L.239.238; 1.L.239.239; 1.L.239.154; 1.L.239.157; 1.L.239.166; 1.L.239.169; 1.L.239.172; 1.L.239.175; 1.L.239.240; 1.L.239.244; 1.L.154.228; 1.L.154.229; 1.L.154.230; 1.L.154.231; 1.L.154.236; 1.L.154.237; 1.L.154.238; 1.L.154.239; 1.L.154.154; 1.L.154.157; 1.L.154.166; 1.L.154.169; 1.L.154.172; 1.L.154.175; 1.L.154.240; 1.L.154.244; 1.L.157.228; 1.L.157.229; 1.L.157.230; 1.L.157.231; 1.L.157.236; 1.L.157.237; 1.L.157.238; 1.L.157.239; 1.L.157.154; 1.L.157.157; 1.L.157.166; 1.L.157.169; 1.L.157.172; 1.L.157.175; 1.L.157.240; 1.L.157.244; 1.L.166.228; 1.L.166.229; 1.L.166.230; 1.L.166.231; 1.L.166.236; 1.L.166.237; 1.L.166.238; 1.L.166.239; 1.L.166.154; 1.L.166.157; 1.L.166.166; 1.L.166.169; 1.L.166.172; 1.L.166.175; 1.L.166.240; 1.L.166.244; 1.L.169.228; 1.L.169.229; 1.L.169.230; 1.L.169.231; 1.L.169.236; 1.L.169.237; 1.L.169.238; 1.L.169.239; 1.L.169.154; 1.L.169.157; 1.L.169.166; 1.L.169.169; 1.L.169.172; 1.L.169.175; 1.L.169.240; 1.L.169.244; 1.L.172.228; 1.L.172.229; 1.L.172.230; 1.L.172.231; 1.L.172.236; 1.L.172.237; 1.L.172.238; 1.L.172.239; 1.L.172.154; 1.L.172.157; 1.L.172.166; 1.L.172.169; 1.L.172.172; 1.L.172.175; 1.L.172.240; 1.L.172.244; 1.L.175.228; 1.L.175.229; 1.L.175.230; 1.L.175.231; 1.L.175.236; 1.L.175.237; 1.L.175.238; 1.L.175.239; 1.L.175.154; 1.L.175.157; 1.L.175.166; 1.L.175.169; 1.L.175.172; 1.L.175.175; 1.L.175.240; 1.L.175.244; 1.L.240.228; 1.L.240.229; 1.L.240.230; 1.L.240.231; 1.L.240.236; 1.L.240.237; 1.L.240.238; 1.L.240.239; 1.L.240.154;

1.L.240.157; 1.L.240.166; 1.L.240.169; 1.L.240.172; 1.L.240.175; 1.L.240.240; 1.L.240.244; 1.L.244.228; 1.L.244.229; 1.L.244.230; 1.L.244.231; 1.L.244.236; 1.L.244.237; 1.L.244.238; 1.L.244.239; 1.L.244.154; 1.L.244.157; 1.L.244.166; 1.L.244.169; 1.L.244.172; 1.L.244.175; 1.L.244.240; 1.L.244.244;

Prodrugs of 1.O

1.O.228.228; 1.O.228.229; 1.O.228.230; 1.O.228.231; 1.O.228.236; 1.O.228.237; 1.O.228.238; 1.O.228.239; 1.O.228.154; 1.O.228.157; 1.O.228.166; 1.O.228.169; 1.O.228.172; 1.O.228.175; 1.O.228.240; 1.O.228.244; 1.O.229.228; 1.O.229.229; 1.O.229.230; 1.O.229.231; 1.O.229.236; 1.O.229.237; 1.O.229.238; 1.O.229.239; 1.O.229.154; 1.O.229.157; 1.O.229.166; 1.O.229.169; 1.O.229.172; 1.O.229.175; 1.O.229.240; 1.O.229.244; 1.O.230.228; 1.O.230.229; 1.O.230.230; 1.O.230.231; 1.O.230.236; 1.O.230.237; 1.O.230.238; 1.O.230.239; 1.O.230.154; 1.O.230.157; 1.O.230.166; 1.O.230.169; 1.O.230.172; 1.O.230.175; 1.O.230.240; 1.O.230.244; 1.O.231.228; 1.O.231.229; 1.O.231.230; 1.O.231.231; 1.O.231.236; 1.O.231.237; 1.O.231.238; 1.O.231.239; 1.O.231.154; 1.O.231.157; 1.O.231.166; 1.O.231.169; 1.O.231.172; 1.O.231.175; 1.O.231.240; 1.O.231.244; 1.O.236.228; 1.O.236.229; 1.O.236.230; 1.O.236.231; 1.O.236.236; 1.O.236.237; 1.O.236.238; 1.O.236.239; 1.O.236.154; 1.O.236.157; 1.O.236.166; 1.O.236.169; 1.O.236.172; 1.O.236.175; 1.O.236.240; 1.O.236.244; 1.O.237.228; 1.O.237.229; 1.O.237.230; 1.O.237.231; 1.O.237.236; 1.O.237.237; 1.O.237.238; 1.O.237.239; 1.O.237.154; 1.O.237.157; 1.O.237.166; 1.O.237.169; 1.O.237.172; 1.O.237.175; 1.O.237.240; 1.O.237.244; 1.O.238.228; 1.O.238.229; 1.O.238.230; 1.O.238.231; 1.O.238.236; 1.O.238.237; 1.O.238.238; 1.O.238.239; 1.O.238.154; 1.O.238.157; 1.O.238.166; 1.O.238.169; 1.O.238.172; 1.O.238.175; 1.O.238.240; 1.O.238.244; 1.O.239.228; 1.O.239.229; 1.O.239.230; 1.O.239.231; 1.O.239.236; 1.O.239.237; 1.O.239.238; 1.O.239.239;

1.O.239.154; 1.O.239.157; 1.O.239.166; 1.O.239.169; 1.O.239.172; 1.O.239.175; 1.O.239.240; 1.O.239.244; 1.O.154.228; 1.O.154.229; 1.O.154.230; 1.O.154.231; 1.O.154.236; 1.O.154.237; 1.O.154.238; 1.O.154.239; 1.O.154.154; 1.O.154.157; 1.O.154.166; 1.O.154.169; 1.O.154.172; 1.O.154.175; 1.O.154.240; 1.O.154.244; 1.O.157.228; 1.O.157.229; 1.O.157.230; 1.O.157.231; 1.O.157.236; 1.O.157.237; 1.O.157.238; 1.O.157.239; 1.O.157.154; 1.O.157.157; 1.O.157.166; 1.O.157.169; 1.O.157.172; 1.O.157.175; 1.O.157.240; 1.O.157.244; 1.O.166.228; 1.O.166.229; 1.O.166.230; 1.O.166.231; 1.O.166.236; 1.O.166.237; 1.O.166.238; 1.O.166.239; 1.O.166.154; 1.O.166.157; 1.O.166.166; 1.O.166.169; 1.O.166.172; 1.O.166.175; 1.O.166.240; 1.O.166.244; 1.O.169.228; 1.O.169.229; 1.O.169.230; 1.O.169.231; 1.O.169.236; 1.O.169.237; 1.O.169.238; 1.O.169.239; 1.O.169.154; 1.O.169.157; 1.O.169.166; 1.O.169.169; 1.O.169.172; 1.O.169.175; 1.O.169.240; 1.O.169.244; 1.O.172.228; 1.O.172.229; 1.O.172.230; 1.O.172.231; 1.O.172.236; 1.O.172.237; 1.O.172.238; 1.O.172.239; 1.O.172.154; 1.O.172.157; 1.O.172.166; 1.O.172.169; 1.O.172.172; 1.O.172.175; 1.O.172.240; 1.O.172.244; 1.O.175.228; 1.O.175.229; 1.O.175.230; 1.O.175.231; 1.O.175.236; 1.O.175.237; 1.O.175.238; 1.O.175.239; 1.O.175.154; 1.O.175.157; 1.O.175.166; 1.O.175.169; 1.O.175.172; 1.O.175.175; 1.O.175.240; 1.O.175.244; 1.O.240.228; 1.O.240.229; 1.O.240.230; 1.O.240.231; 1.O.240.236; 1.O.240.237; 1.O.240.238; 1.O.240.239; 1.O.240.154; 1.O.240.157; 1.O.240.166; 1.O.240.169; 1.O.240.172; 1.O.240.175; 1.O.240.240; 1.O.240.244; 1.O.244.228; 1.O.244.229; 1.O.244.230; 1.O.244.231; 1.O.244.236; 1.O.244.237; 1.O.244.238; 1.O.244.239; 1.O.244.154; 1.O.244.157; 1.O.244.166; 1.O.244.169; 1.O.244.172; 1.O.244.175; 1.O.244.240; 1.O.244.244;

Prodrugs of 1.P

1.P.228.228; 1.P.228.229; 1.P.228.230; 1.P.228.231; 1.P.228.236; 1.P.228.237; 1.P.228.238; 1.P.228.239; 1.P.228.154; 1.P.228.157; 1.P.228.166; 1.P.228.169; 1.P.228.172; 1.P.228.175; 1.P.228.240; 1.P.228.244; 1.P.229.228; 1.P.229.229; 1.P.229.230; 1.P.229.231; 1.P.229.236; 1.P.229.237; 1.P.229.238; 1.P.229.239; 1.P.229.154; 1.P.229.157; 1.P.229.166; 1.P.229.169; 1.P.229.172; 1.P.229.175; 1.P.229.240; 1.P.229.244; 1.P.230.228; 1.P.230.229; 1.P.230.230; 1.P.230.231; 1.P.230.236; 1.P.230.237; 1.P.230.238; 1.P.230.239; 1.P.230.154; 1.P.230.157; 1.P.230.166; 1.P.230.169; 1.P.230.172; 1.P.230.175; 1.P.230.240; 1.P.230.244; 1.P.231.228; 1.P.231.229; 1.P.231.230; 1.P.231.231; 1.P.231.236; 1.P.231.237; 1.P.231.238; 1.P.231.239; 1.P.231.154; 1.P.231.157; 1.P.231.166; 1.P.231.169; 1.P.231.172; 1.P.231.175; 1.P.231.240; 1.P.231.244; 1.P.236.228; 1.P.236.229; 1.P.236.230; 1.P.236.231; 1.P.236.236; 1.P.236.237; 1.P.236.238; 1.P.236.239; 1.P.236.154; 1.P.236.157; 1.P.236.166; 1.P.236.169; 1.P.236.172; 1.P.236.175; 1.P.236.240; 1.P.236.244; 1.P.237.228; 1.P.237.229; 1.P.237.230; 1.P.237.231; 1.P.237.236; 1.P.237.237; 1.P.237.238; 1.P.237.239; 1.P.237.154; 1.P.237.157; 1.P.237.166; 1.P.237.169; 1.P.237.172; 1.P.237.175; 1.P.237.240; 1.P.237.244; 1.P.238.228; 1.P.238.229; 1.P.238.230; 1.P.238.231; 1.P.238.236; 1.P.238.237; 1.P.238.238; 1.P.238.239; 1.P.238.154; 1.P.238.157; 1.P.238.166; 1.P.238.169; 1.P.238.172; 1.P.238.175; 1.P.238.240; 1.P.238.244; 1.P.239.228; 1.P.239.229; 1.P.239.230; 1.P.239.231; 1.P.239.236; 1.P.239.237; 1.P.239.238; 1.P.239.239; 1.P.239.154; 1.P.239.157; 1.P.239.166; 1.P.239.169; 1.P.239.172; 1.P.239.175; 1.P.239.240; 1.P.239.244; 1.P.154.228; 1.P.154.229; 1.P.154.230; 1.P.154.231; 1.P.154.236; 1.P.154.237; 1.P.154.238; 1.P.154.239; 1.P.154.154; 1.P.154.157; 1.P.154.166; 1.P.154.169; 1.P.154.172; 1.P.154.175; 1.P.154.240; 1.P.154.244; 1.P.157.228; 1.P.157.229; 1.P.157.230; 1.P.157.231; 1.P.157.236; 1.P.157.237; 1.P.157.238; 1.P.157.239; 1.P.157.154; 1.P.157.157; 1.P.157.166; 1.P.157.169; 1.P.157.172; 1.P.157.175; 1.P.157.240; 1.P.157.244; 1.P.166.228; 1.P.166.229; 1.P.166.230; 1.P.166.231; 1.P.166.236; 1.P.166.237; 1.P.166.238; 1.P.166.239; 1.P.166.154; 1.P.166.157; 1.P.166.166; 1.P.166.169; 1.P.166.172; 1.P.166.175; 1.P.166.240; 1.P.166.244; 1.P.169.228; 1.P.169.229; 1.P.169.230;

1.P.169.231; 1.P.169.236; 1.P.169.237; 1.P.169.238; 1.P.169.239; 1.P.169.154; 1.P.169.157; 1.P.169.166; 1.P.169.169; 1.P.169.172; 1.P.169.175; 1.P.169.240; 1.P.169.244; 1.P.172.228; 1.P.172.229; 1.P.172.230; 1.P.172.231; 1.P.172.236; 1.P.172.237; 1.P.172.238; 1.P.172.239; 1.P.172.154; 1.P.172.157; 1.P.172.166; 1.P.172.169; 1.P.172.172; 1.P.172.175; 1.P.172.240; 1.P.172.244; 1.P.175.228; 1.P.175.229; 1.P.175.230; 1.P.175.231; 1.P.175.236; 1.P.175.237; 1.P.175.238; 1.P.175.239; 1.P.175.154; 1.P.175.157; 1.P.175.166; 1.P.175.169; 1.P.175.172; 1.P.175.175; 1.P.175.240; 1.P.175.244; 1.P.240.228; 1.P.240.229; 1.P.240.230; 1.P.240.231; 1.P.240.236; 1.P.240.237; 1.P.240.238; 1.P.240.239; 1.P.240.154; 1.P.240.157; 1.P.240.166; 1.P.240.169; 1.P.240.172; 1.P.240.175; 1.P.240.240; 1.P.240.244; 1.P.244.228; 1.P.244.229; 1.P.244.230; 1.P.244.231; 1.P.244.236; 1.P.244.237; 1.P.244.238; 1.P.244.239; 1.P.244.154; 1.P.244.157; 1.P.244.166; 1.P.244.169; 1.P.244.172; 1.P.244.175; 1.P.244.240; 1.P.244.244;

Prodrugs of 1.U

1.U.228.228; 1.U.228.229; 1.U.228.230; 1.U.228.231; 1.U.228.236; 1.U.228.237; 1.U.228.238; 1.U.228.239; 1.U.228.154; 1.U.228.157; 1.U.228.166; 1.U.228.169; 1.U.228.172; 1.U.228.175; 1.U.228.240; 1.U.228.244; 1.U.229.228; 1.U.229.229; 1.U.229.230; 1.U.229.231; 1.U.229.236; 1.U.229.237; 1.U.229.238; 1.U.229.239; 1.U.229.154; 1.U.229.157; 1.U.229.166; 1.U.229.169; 1.U.229.172; 1.U.229.175; 1.U.229.240; 1.U.229.244; 1.U.230.228; 1.U.230.229; 1.U.230.230; 1.U.230.231; 1.U.230.236; 1.U.230.237; 1.U.230.238; 1.U.230.239; 1.U.230.154; 1.U.230.157; 1.U.230.166; 1.U.230.169; 1.U.230.172; 1.U.230.175; 1.U.230.240; 1.U.230.244; 1.U.231.228; 1.U.231.229; 1.U.231.230; 1.U.231.231; 1.U.231.236; 1.U.231.237; 1.U.231.238; 1.U.231.239; 1.U.231.154; 1.U.231.157; 1.U.231.166; 1.U.231.169; 1.U.231.172; 1.U.231.175; 1.U.231.240; 1.U.231.244; 1.U.236.228; 1.U.236.229; 1.U.236.230; 1.U.236.231; 1.U.236.236; 1.U.236.237; 1.U.236.238; 1.U.236.239; 1.U.236.154; 1.U.236.157; 1.U.236.166;

1.U.236.169; 1.U.236.172; 1.U.236.175; 1.U.236.240; 1.U.236.244; 1.U.237.228; 1.U.237.229; 1.U.237.230; 1.U.237.231; 1.U.237.236; 1.U.237.237; 1.U.237.238; 1.U.237.239; 1.U.237.154; 1.U.237.157; 1.U.237.166; 1.U.237.169; 1.U.237.172; 1.U.237.175; 1.U.237.240; 1.U.237.244; 1.U.238.228; 1.U.238.229; 1.U.238.230; 1.U.238.231; 1.U.238.236; 1.U.238.237; 1.U.238.238; 1.U.238.239; 1.U.238.154; 1.U.238.157; 1.U.238.166; 1.U.238.169; 1.U.238.172; 1.U.238.175; 1.U.238.240; 1.U.238.244; 1.U.239.228; 1.U.239.229; 1.U.239.230; 1.U.239.231; 1.U.239.236; 1.U.239.237; 1.U.239.238; 1.U.239.239; 1.U.239.154; 1.U.239.157; 1.U.239.166; 1.U.239.169; 1.U.239.172; 1.U.239.175; 1.U.239.240; 1.U.239.244; 1.U.154.228; 1.U.154.229; 1.U.154.230; 1.U.154.231; 1.U.154.236; 1.U.154.237; 1.U.154.238; 1.U.154.239; 1.U.154.154; 1.U.154.157; 1.U.154.166; 1.U.154.169; 1.U.154.172; 1.U.154.175; 1.U.154.240; 1.U.154.244; 1.U.157.228; 1.U.157.229; 1.U.157.230; 1.U.157.231; 1.U.157.236; 1.U.157.237; 1.U.157.238; 1.U.157.239; 1.U.157.154; 1.U.157.157; 1.U.157.166; 1.U.157.169; 1.U.157.172; 1.U.157.175; 1.U.157.240; 1.U.157.244; 1.U.166.228; 1.U.166.229; 1.U.166.230; 1.U.166.231; 1.U.166.236; 1.U.166.237; 1.U.166.238; 1.U.166.239; 1.U.166.154; 1.U.166.157; 1.U.166.166; 1.U.166.169; 1.U.166.172; 1.U.166.175; 1.U.166.240; 1.U.166.244; 1.U.169.228; 1.U.169.229; 1.U.169.230; 1.U.169.231; 1.U.169.236; 1.U.169.237; 1.U.169.238; 1.U.169.239; 1.U.169.154; 1.U.169.157; 1.U.169.166; 1.U.169.169; 1.U.169.172; 1.U.169.175; 1.U.169.240; 1.U.169.244; 1.U.172.228; 1.U.172.229; 1.U.172.230; 1.U.172.231; 1.U.172.236; 1.U.172.237; 1.U.172.238; 1.U.172.239; 1.U.172.154; 1.U.172.157; 1.U.172.166; 1.U.172.169; 1.U.172.172; 1.U.172.175; 1.U.172.240; 1.U.172.244; 1.U.175.228; 1.U.175.229; 1.U.175.230; 1.U.175.231; 1.U.175.236; 1.U.175.237; 1.U.175.238; 1.U.175.239; 1.U.175.154; 1.U.175.157; 1.U.175.166; 1.U.175.169; 1.U.175.172; 1.U.175.175; 1.U.175.240; 1.U.175.244; 1.U.240.228;

1.U.240.229; 1.U.240.230; 1.U.240.231; 1.U.240.236; 1.U.240.237; 1.U.240.238; 1.U.240.239; 1.U.240.154; 1.U.240.157; 1.U.240.166; 1.U.240.169; 1.U.240.172; 1.U.240.175; 1.U.240.240; 1.U.240.244; 1.U.244.228; 1.U.244.229; 1.U.244.230; 1.U.244.231; 1.U.244.236; 1.U.244.237; 1.U.244.238; 1.U.244.239; 1.U.244.154; 1.U.244.157; 1.U.244.166; 1.U.244.169; 1.U.244.172; 1.U.244.175; 1.U.244.240; 1.U.244.244;

Prodrugs of 1.W

1.W.228.228; 1.W.228.229; 1.W.228.230; 1.W.228.231; 1.W.228.236; 1.W.228.237; 1.W.228.238; 1.W.228.239; 1.W.228.154; 1.W.228.157; 1.W.228.166; 1.W.228.169; 1.W.228.172; 1.W.228.175; 1.W.228.240; 1.W.228.244; 1.W.229.228; 1.W.229.229; 1.W.229.230; 1.W.229.231; 1.W.229.236; 1.W.229.237; 1.W.229.238; 1.W.229.239; 1.W.229.154; 1.W.229.157; 1.W.229.166; 1.W.229.169; 1.W.229.172; 1.W.229.175; 1.W.229.240; 1.W.229.244; 1.W.230.228; 1.W.230.229; 1.W.230.230; 1.W.230.231; 1.W.230.236; 1.W.230.237; 1.W.230.238; 1.W.230.239; 1.W.230.154; 1.W.230.157; 1.W.230.166; 1.W.230.169; 1.W.230.172; 1.W.230.175; 1.W.230.240; 1.W.230.244; 1.W.231.228; 1.W.231.229; 1.W.231.230; 1.W.231.231; 1.W.231.236; 1.W.231.237; 1.W.231.238; 1.W.231.239; 1.W.231.154; 1.W.231.157; 1.W.231.166; 1.W.231.169; 1.W.231.172; 1.W.231.175; 1.W.231.240; 1.W.231.244; 1.W.236.228; 1.W.236.229; 1.W.236.230; 1.W.236.231; 1.W.236.236; 1.W.236.237; 1.W.236.238; 1.W.236.239; 1.W.236.154; 1.W.236.157; 1.W.236.166; 1.W.236.169; 1.W.236.172; 1.W.236.175; 1.W.236.240; 1.W.236.244; 1.W.237.228; 1.W.237.229; 1.W.237.230; 1.W.237.231; 1.W.237.236; 1.W.237.237; 1.W.237.238; 1.W.237.239; 1.W.237.154; 1.W.237.157; 1.W.237.166; 1.W.237.169; 1.W.237.172; 1.W.237.175; 1.W.237.240; 1.W.237.244; 1.W.238.228; 1.W.238.229; 1.W.238.230; 1.W.238.231; 1.W.238.236; 1.W.238.237; 1.W.238.238; 1.W.238.239; 1.W.238.154;

1.W.238.157; 1.W.238.166; 1.W.238.169; 1.W.238.172; 1.W.238.175; 1.W.238.240; 1.W.238.244; 1.W.239.228; 1.W.239.229; 1.W.239.230; 1.W.239.231; 1.W.239.236; 1.W.239.237; 1.W.239.238; 1.W.239.239; 1.W.239.154; 1.W.239.157; 1.W.239.166; 1.W.239.169; 1.W.239.172; 1.W.239.175; 1.W.239.240; 1.W.239.244; 1.W.154.228; 1.W.154.229; 1.W.154.230; 1.W.154.231; 1.W.154.236; 1.W.154.237; 1.W.154.238; 1.W.154.239; 1.W.154.154; 1.W.154.157; 1.W.154.166; 1.W.154.169; 1.W.154.172; 1.W.154.175; 1.W.154.240; 1.W.154.244; 1.W.157.228; 1.W.157.229; 1.W.157.230; 1.W.157.231; 1.W.157.236; 1.W.157.237; 1.W.157.238; 1.W.157.239; 1.W.157.154; 1.W.157.157; 1.W.157.166; 1.W.157.169; 1.W.157.172; 1.W.157.175; 1.W.157.240; 1.W.157.244; 1.W.166.228; 1.W.166.229; 1.W.166.230; 1.W.166.231; 1.W.166.236; 1.W.166.237; 1.W.166.238; 1.W.166.239; 1.W.166.154; 1.W.166.157; 1.W.166.166; 1.W.166.169; 1.W.166.172; 1.W.166.175; 1.W.166.240; 1.W.166.244; 1.W.169.228; 1.W.169.229; 1.W.169.230; 1.W.169.231; 1.W.169.236; 1.W.169.237; 1.W.169.238; 1.W.169.239; 1.W.169.154; 1.W.169.157; 1.W.169.166; 1.W.169.169; 1.W.169.172; 1.W.169.175; 1.W.169.240; 1.W.169.244; 1.W.172.228; 1.W.172.229; 1.W.172.230; 1.W.172.231; 1.W.172.236; 1.W.172.237; 1.W.172.238; 1.W.172.239; 1.W.172.154; 1.W.172.157; 1.W.172.166; 1.W.172.169; 1.W.172.172; 1.W.172.175; 1.W.172.240; 1.W.172.244; 1.W.175.228; 1.W.175.229; 1.W.175.230; 1.W.175.231; 1.W.175.236; 1.W.175.237; 1.W.175.238; 1.W.175.239; 1.W.175.154; 1.W.175.157; 1.W.175.166; 1.W.175.169; 1.W.175.172; 1.W.175.175; 1.W.175.240; 1.W.175.244; 1.W.240.228; 1.W.240.229; 1.W.240.230; 1.W.240.231; 1.W.240.236; 1.W.240.237; 1.W.240.238; 1.W.240.239; 1.W.240.154; 1.W.240.157; 1.W.240.166; 1.W.240.169; 1.W.240.172; 1.W.240.175; 1.W.240.240; 1.W.240.244; 1.W.244.228; 1.W.244.229; 1.W.244.230; 1.W.244.231; 1.W.244.236; 1.W.244.237; 1.W.244.238; 1.W.244.239; 1.W.244.154; 1.W.244.157;

1.W.244.166; 1.W.244.169; 1.W.244.172; 1.W.244.175; 1.W.244.240; 1.W.244.244;

Prodrugs of 1.Y

1.Y.228.228; 1.Y.228.229; 1.Y.228.230; 1.Y.228.231; 1.Y.228.236; 1.Y.228.237; 1.Y.228.238; 1.Y.228.239; 1.Y.228.154; 1.Y.228.157; 1.Y.228.166; 1.Y.228.169; 1.Y.228.172; 1.Y.228.175; 1.Y.228.240; 1.Y.228.244; 1.Y.229.228; 1.Y.229.229; 1.Y.229.230; 1.Y.229.231; 1.Y.229.236; 1.Y.229.237; 1.Y.229.238; 1.Y.229.239; 1.Y.229.154; 1.Y.229.157; 1.Y.229.166; 1.Y.229.169; 1.Y.229.172; 1.Y.229.175; 1.Y.229.240; 1.Y.229.244; 1.Y.230.228; 1.Y.230.229; 1.Y.230.230; 1.Y.230.231; 1.Y.230.236; 1.Y.230.237; 1.Y.230.238; 1.Y.230.239; 1.Y.230.154; 1.Y.230.157; 1.Y.230.166; 1.Y.230.169; 1.Y.230.172; 1.Y.230.175; 1.Y.230.240; 1.Y.230.244; 1.Y.231.228; 1.Y.231.229; 1.Y.231.230; 1.Y.231.231; 1.Y.231.236; 1.Y.231.237; 1.Y.231.238; 1.Y.231.239; 1.Y.231.154; 1.Y.231.157; 1.Y.231.166; 1.Y.231.169; 1.Y.231.172; 1.Y.231.175; 1.Y.231.240; 1.Y.231.244; 1.Y.236.228; 1.Y.236.229; 1.Y.236.230; 1.Y.236.231; 1.Y.236.236; 1.Y.236.237; 1.Y.236.238; 1.Y.236.239; 1.Y.236.154; 1.Y.236.157; 1.Y.236.166; 1.Y.236.169; 1.Y.236.172; 1.Y.236.175; 1.Y.236.240; 1.Y.236.244; 1.Y.237.228; 1.Y.237.229; 1.Y.237.230; 1.Y.237.231; 1.Y.237.236; 1.Y.237.237; 1.Y.237.238; 1.Y.237.239; 1.Y.237.154; 1.Y.237.157; 1.Y.237.166; 1.Y.237.169; 1.Y.237.172; 1.Y.237.175; 1.Y.237.240; 1.Y.237.244; 1.Y.238.228; 1.Y.238.229; 1.Y.238.230; 1.Y.238.231; 1.Y.238.236; 1.Y.238.237; 1.Y.238.238; 1.Y.238.239; 1.Y.238.154; 1.Y.238.157; 1.Y.238.166; 1.Y.238.169; 1.Y.238.172; 1.Y.238.175; 1.Y.238.240; 1.Y.238.244; 1.Y.239.228; 1.Y.239.229; 1.Y.239.230; 1.Y.239.231; 1.Y.239.236; 1.Y.239.237; 1.Y.239.238; 1.Y.239.239; 1.Y.239.154; 1.Y.239.157; 1.Y.239.166; 1.Y.239.169; 1.Y.239.172; 1.Y.239.175; 1.Y.239.240; 1.Y.239.244; 1.Y.154.228; 1.Y.154.229; 1.Y.154.230; 1.Y.154.231; 1.Y.154.236; 1.Y.154.237; 1.Y.154.238; 1.Y.154.239; 1.Y.154.154; 1.Y.154.157; 1.Y.154.166; 1.Y.154.169; 1.Y.154.172; 1.Y.154.175; 1.Y.154.240; 1.Y.154.244; 1.Y.157.228; 1.Y.157.229; 1.Y.157.230; 1.Y.157.231; 1.Y.157.236; 1.Y.157.237; 1.Y.157.238; 1.Y.157.239; 1.Y.157.154; 1.Y.157.157; 1.Y.157.166;

1.Y.157.169; 1.Y.157.172; 1.Y.157.175; 1.Y.157.240; 1.Y.157.244; 1.Y.166.228; 1.Y.166.229; 1.Y.166.230; 1.Y.166.231; 1.Y.166.236; 1.Y.166.237; 1.Y.166.238; 1.Y.166.239; 1.Y.166.154; 1.Y.166.157; 1.Y.166.166; 1.Y.166.169; 1.Y.166.172; 1.Y.166.175; 1.Y.166.240; 1.Y.166.244; 1.Y.169.228; 1.Y.169.229; 1.Y.169.230; 1.Y.169.231; 1.Y.169.236; 1.Y.169.237; 1.Y.169.238; 1.Y.169.239; 1.Y.169.154; 1.Y.169.157; 1.Y.169.166; 1.Y.169.169; 1.Y.169.172; 1.Y.169.175; 1.Y.169.240; 1.Y.169.244; 1.Y.172.228; 1.Y.172.229; 1.Y.172.230; 1.Y.172.231; 1.Y.172.236; 1.Y.172.237; 1.Y.172.238; 1.Y.172.239; 1.Y.172.154; 1.Y.172.157; 1.Y.172.166; 1.Y.172.169; 1.Y.172.172; 1.Y.172.175; 1.Y.172.240; 1.Y.172.244; 1.Y.175.228; 1.Y.175.229; 1.Y.175.230; 1.Y.175.231; 1.Y.175.236; 1.Y.175.237; 1.Y.175.238; 1.Y.175.239; 1.Y.175.154; 1.Y.175.157; 1.Y.175.166; 1.Y.175.169; 1.Y.175.172; 1.Y.175.175; 1.Y.175.240; 1.Y.175.244; 1.Y.240.228; 1.Y.240.229; 1.Y.240.230; 1.Y.240.231; 1.Y.240.236; 1.Y.240.237; 1.Y.240.238; 1.Y.240.239; 1.Y.240.154; 1.Y.240.157; 1.Y.240.166; 1.Y.240.169; 1.Y.240.172; 1.Y.240.175; 1.Y.240.240; 1.Y.240.244; 1.Y.244.228; 1.Y.244.229; 1.Y.244.230; 1.Y.244.231; 1.Y.244.236; 1.Y.244.237; 1.Y.244.238; 1.Y.244.239; 1.Y.244.154; 1.Y.244.157; 1.Y.244.166; 1.Y.244.169; 1.Y.244.172; 1.Y.244.175; 1.Y.244.240; 1.Y.244.244;

Prodrugs of 2.B

2.B.228.228; 2.B.228.229; 2.B.228.230; 2.B.228.231; 2.B.228.236; 2.B.228.237; 2.B.228.238; 2.B.228.239; 2.B.228.154; 2.B.228.157; 2.B.228.166; 2.B.228.169; 2.B.228.172; 2.B.228.175; 2.B.228.240; 2.B.228.244; 2.B.229.228; 2.B.229.229; 2.B.229.230; 2.B.229.231; 2.B.229.236; 2.B.229.237; 2.B.229.238; 2.B.229.239; 2.B.229.154; 2.B.229.157; 2.B.229.166; 2.B.229.169; 2.B.229.172; 2.B.229.175; 2.B.229.240; 2.B.229.244; 2.B.230.228; 2.B.230.229; 2.B.230.230; 2.B.230.231; 2.B.230.236; 2.B.230.237; 2.B.230.238; 2.B.230.239; 2.B.230.154; 2.B.230.157; 2.B.230.166; 2.B.230.169; 2.B.230.172; 2.B.230.175; 2.B.230.240; 2.B.230.244; 2.B.231.228; 2.B.231.229; 2.B.231.230; 2.B.231.231; 2.B.231.236; 2.B.231.237; 2.B.231.238; 2.B.231.239; 2.B.231.154; 2.B.231.157; 2.B.231.166; 2.B.231.169; 2.B.231.172; 2.B.231.175; 2.B.231.240; 2.B.231.244; 2.B.236.228;

2.B.236.229; 2.B.236.230; 2.B.236.231; 2.B.236.236; 2.B.236.237; 2.B.236.238; 2.B.236.239; 2.B.236.154; 2.B.236.157; 2.B.236.166; 2.B.236.169; 2.B.236.172; 2.B.236.175; 2.B.236.240; 2.B.236.244; 2.B.237.228; 2.B.237.229; 2.B.237.230; 2.B.237.231; 2.B.237.236; 2.B.237.237; 2.B.237.238; 2.B.237.239; 2.B.237.154; 2.B.237.157; 2.B.237.166; 2.B.237.169; 2.B.237.172; 2.B.237.175; 2.B.237.240; 2.B.237.244; 2.B.238.228; 2.B.238.229; 2.B.238.230; 2.B.238.231; 2.B.238.236; 2.B.238.237; 2.B.238.238; 2.B.238.239; 2.B.238.154; 2.B.238.157; 2.B.238.166; 2.B.238.169; 2.B.238.172; 2.B.238.175; 2.B.238.240; 2.B.238.244; 2.B.239.228; 2.B.239.229; 2.B.239.230; 2.B.239.231; 2.B.239.236; 2.B.239.237; 2.B.239.238; 2.B.239.239; 2.B.239.154; 2.B.239.157; 2.B.239.166; 2.B.239.169; 2.B.239.172; 2.B.239.175; 2.B.239.240; 2.B.239.244; 2.B.154.228; 2.B.154.229; 2.B.154.230; 2.B.154.231; 2.B.154.236; 2.B.154.237; 2.B.154.238; 2.B.154.239; 2.B.154.154; 2.B.154.157; 2.B.154.166; 2.B.154.169; 2.B.154.172; 2.B.154.175; 2.B.154.240; 2.B.154.244; 2.B.157.228; 2.B.157.229; 2.B.157.230; 2.B.157.231; 2.B.157.236; 2.B.157.237; 2.B.157.238; 2.B.157.239; 2.B.157.154; 2.B.157.157; 2.B.157.166; 2.B.157.169; 2.B.157.172; 2.B.157.175; 2.B.157.240; 2.B.157.244; 2.B.166.228; 2.B.166.229; 2.B.166.230; 2.B.166.231; 2.B.166.236; 2.B.166.237; 2.B.166.238; 2.B.166.239; 2.B.166.154; 2.B.166.157; 2.B.166.166; 2.B.166.169; 2.B.166.172; 2.B.166.175; 2.B.166.240; 2.B.166.244; 2.B.169.228; 2.B.169.229; 2.B.169.230; 2.B.169.231; 2.B.169.236; 2.B.169.237; 2.B.169.238; 2.B.169.239; 2.B.169.154; 2.B.169.157; 2.B.169.166; 2.B.169.169; 2.B.169.172; 2.B.169.175; 2.B.169.240; 2.B.169.244; 2.B.172.228; 2.B.172.229; 2.B.172.230; 2.B.172.231; 2.B.172.236; 2.B.172.237; 2.B.172.238; 2.B.172.239; 2.B.172.154; 2.B.172.157; 2.B.172.166; 2.B.172.169; 2.B.172.172; 2.B.172.175; 2.B.172.240; 2.B.172.244; 2.B.175.228; 2.B.175.229; 2.B.175.230; 2.B.175.231; 2.B.175.236; 2.B.175.237; 2.B.175.238; 2.B.175.239; 2.B.175.154; 2.B.175.157; 2.B.175.166; 2.B.175.169; 2.B.175.172; 2.B.175.175; 2.B.175.240; 2.B.175.244; 2.B.240.228; 2.B.240.229; 2.B.240.230; 2.B.240.231; 2.B.240.236; 2.B.240.237; 2.B.240.238; 2.B.240.239; 2.B.240.154; 2.B.240.157; 2.B.240.166; 2.B.240.169; 2.B.240.172; 2.B.240.175; 2.B.240.240; 2.B.240.244; 2.B.244.228; 2.B.244.229; 2.B.244.230; 2.B.244.231; 2.B.244.236;

2.B.244.237; 2.B.244.238; 2.B.244.239; 2.B.244.154; 2.B.244.157; 2.B.244.166; 2.B.244.169; 2.B.244.172; 2.B.244.175; 2.B.244.240; 2.B.244.244;

Prodrugs of 2.D

2.D.228.228; 2.D.228.229; 2.D.228.230; 2.D.228.231; 2.D.228.236; 2.D.228.237; 2.D.228.238; 2.D.228.239; 2.D.228.154; 2.D.228.157; 2.D.228.166; 2.D.228.169; 2.D.228.172; 2.D.228.175; 2.D.228.240; 2.D.228.244; 2.D.229.228; 2.D.229.229; 2.D.229.230; 2.D.229.231; 2.D.229.236; 2.D.229.237; 2.D.229.238; 2.D.229.239; 2.D.229.154; 2.D.229.157; 2.D.229.166; 2.D.229.169; 2.D.229.172; 2.D.229.175; 2.D.229.240; 2.D.229.244; 2.D.230.228; 2.D.230.229; 2.D.230.230; 2.D.230.231; 2.D.230.236; 2.D.230.237; 2.D.230.238; 2.D.230.239; 2.D.230.154; 2.D.230.157; 2.D.230.166; 2.D.230.169; 2.D.230.172; 2.D.230.175; 2.D.230.240; 2.D.230.244; 2.D.231.228; 2.D.231.229; 2.D.231.230; 2.D.231.231; 2.D.231.236; 2.D.231.237; 2.D.231.238; 2.D.231.239; 2.D.231.154; 2.D.231.157; 2.D.231.166; 2.D.231.169; 2.D.231.172; 2.D.231.175; 2.D.231.240; 2.D.231.244; 2.D.236.228; 2.D.236.229; 2.D.236.230; 2.D.236.231; 2.D.236.236; 2.D.236.237; 2.D.236.238; 2.D.236.239; 2.D.236.154; 2.D.236.157; 2.D.236.166; 2.D.236.169; 2.D.236.172; 2.D.236.175; 2.D.236.240; 2.D.236.244; 2.D.237.228; 2.D.237.229; 2.D.237.230; 2.D.237.231; 2.D.237.236; 2.D.237.237; 2.D.237.238; 2.D.237.239; 2.D.237.154; 2.D.237.157; 2.D.237.166; 2.D.237.169; 2.D.237.172; 2.D.237.175; 2.D.237.240; 2.D.237.244; 2.D.238.228; 2.D.238.229; 2.D.238.230; 2.D.238.231; 2.D.238.236; 2.D.238.237; 2.D.238.238; 2.D.238.239; 2.D.238.154; 2.D.238.157; 2.D.238.166; 2.D.238.169; 2.D.238.172; 2.D.238.175; 2.D.238.240; 2.D.238.244; 2.D.239.228; 2.D.239.229; 2.D.239.230; 2.D.239.231; 2.D.239.236; 2.D.239.237; 2.D.239.238; 2.D.239.239; 2.D.239.154; 2.D.239.157; 2.D.239.166; 2.D.239.169; 2.D.239.172; 2.D.239.175; 2.D.239.240; 2.D.239.244; 2.D.154.228; 2.D.154.229;

2.D.154.230; 2.D.154.231; 2.D.154.236; 2.D.154.237; 2.D.154.238; 2.D.154.239; 2.D.154.154; 2.D.154.157; 2.D.154.166; 2.D.154.169; 2.D.154.172; 2.D.154.175; 2.D.154.240; 2.D.154.244; 2.D.157.228; 2.D.157.229; 2.D.157.230; 2.D.157.231; 2.D.157.236; 2.D.157.237; 2.D.157.238; 2.D.157.239; 2.D.157.154; 2.D.157.157; 2.D.157.166; 2.D.157.169; 2.D.157.172; 2.D.157.175; 2.D.157.240; 2.D.157.244; 2.D.166.228; 2.D.166.229; 2.D.166.230; 2.D.166.231; 2.D.166.236; 2.D.166.237; 2.D.166.238; 2.D.166.239; 2.D.166.154; 2.D.166.157; 2.D.166.166; 2.D.166.169; 2.D.166.172; 2.D.166.175; 2.D.166.240; 2.D.166.244; 2.D.169.228; 2.D.169.229; 2.D.169.230; 2.D.169.231; 2.D.169.236; 2.D.169.237; 2.D.169.238; 2.D.169.239; 2.D.169.154; 2.D.169.157; 2.D.169.166; 2.D.169.169; 2.D.169.172; 2.D.169.175; 2.D.169.240; 2.D.169.244; 2.D.172.228; 2.D.172.229; 2.D.172.230; 2.D.172.231; 2.D.172.236; 2.D.172.237; 2.D.172.238; 2.D.172.239; 2.D.172.154; 2.D.172.157; 2.D.172.166; 2.D.172.169; 2.D.172.172; 2.D.172.175; 2.D.172.240; 2.D.172.244; 2.D.175.228; 2.D.175.229; 2.D.175.230; 2.D.175.231; 2.D.175.236; 2.D.175.237; 2.D.175.238; 2.D.175.239; 2.D.175.154; 2.D.175.157; 2.D.175.166; 2.D.175.169; 2.D.175.172; 2.D.175.175; 2.D.175.240; 2.D.175.244; 2.D.240.228; 2.D.240.229; 2.D.240.230; 2.D.240.231; 2.D.240.236; 2.D.240.237; 2.D.240.238; 2.D.240.239; 2.D.240.154; 2.D.240.157; 2.D.240.166; 2.D.240.169; 2.D.240.172; 2.D.240.175; 2.D.240.240; 2.D.240.244; 2.D.244.228; 2.D.244.229; 2.D.244.230; 2.D.244.231; 2.D.244.236; 2.D.244.237; 2.D.244.238; 2.D.244.239; 2.D.244.154; 2.D.244.157; 2.D.244.166; 2.D.244.169; 2.D.244.172; 2.D.244.175; 2.D.244.240; 2.D.244.244;

Prodrugs of 2.E

2.E.228.228; 2.E.228.229; 2.E.228.230; 2.E.228.231; 2.E.228.236; 2.E.228.237; 2.E.228.238; 2.E.228.239; 2.E.228.154; 2.E.228.157; 2.E.228.166;

2.E.228.169; 2.E.228.172; 2.E.228.175; 2.E.228.240; 2.E.228.244; 2.E.229.228; 2.E.229.229; 2.E.229.230; 2.E.229.231; 2.E.229.236; 2.E.229.237; 2.E.229.238; 2.E.229.239; 2.E.229.154; 2.E.229.157; 2.E.229.166; 2.E.229.169; 2.E.229.172; 2.E.229.175; 2.E.229.240; 2.E.229.244; 2.E.230.228; 2.E.230.229; 2.E.230.230; 2.E.230.231; 2.E.230.236; 2.E.230.237; 2.E.230.238; 2.E.230.239; 2.E.230.154; 2.E.230.157; 2.E.230.166; 2.E.230.169; 2.E.230.172; 2.E.230.175; 2.E.230.240; 2.E.230.244; 2.E.231.228; 2.E.231.229; 2.E.231.230; 2.E.231.231; 2.E.231.236; 2.E.231.237; 2.E.231.238; 2.E.231.239; 2.E.231.154; 2.E.231.157; 2.E.231.166; 2.E.231.169; 2.E.231.172; 2.E.231.175; 2.E.231.240; 2.E.231.244; 2.E.236.228; 2.E.236.229; 2.E.236.230; 2.E.236.231; 2.E.236.236; 2.E.236.237; 2.E.236.238; 2.E.236.239; 2.E.236.154; 2.E.236.157; 2.E.236.166; 2.E.236.169; 2.E.236.172; 2.E.236.175; 2.E.236.240; 2.E.236.244; 2.E.237.228; 2.E.237.229; 2.E.237.230; 2.E.237.231; 2.E.237.236; 2.E.237.237; 2.E.237.238; 2.E.237.239; 2.E.237.154; 2.E.237.157; 2.E.237.166; 2.E.237.169; 2.E.237.172; 2.E.237.175; 2.E.237.240; 2.E.237.244; 2.E.238.228; 2.E.238.229; 2.E.238.230; 2.E.238.231; 2.E.238.236; 2.E.238.237; 2.E.238.238; 2.E.238.239; 2.E.238.154; 2.E.238.157; 2.E.238.166; 2.E.238.169; 2.E.238.172; 2.E.238.175; 2.E.238.240; 2.E.238.244; 2.E.239.228; 2.E.239.229; 2.E.239.230; 2.E.239.231; 2.E.239.236; 2.E.239.237; 2.E.239.238; 2.E.239.239; 2.E.239.154; 2.E.239.157; 2.E.239.166; 2.E.239.169; 2.E.239.172; 2.E.239.175; 2.E.239.240; 2.E.239.244; 2.E.154.228; 2.E.154.229; 2.E.154.230; 2.E.154.231; 2.E.154.236; 2.E.154.237; 2.E.154.238; 2.E.154.239; 2.E.154.154; 2.E.154.157; 2.E.154.166; 2.E.154.169; 2.E.154.172; 2.E.154.175; 2.E.154.240; 2.E.154.244; 2.E.157.228; 2.E.157.229; 2.E.157.230; 2.E.157.231; 2.E.157.236; 2.E.157.237; 2.E.157.238; 2.E.157.239; 2.E.157.154; 2.E.157.157; 2.E.157.166; 2.E.157.169; 2.E.157.172; 2.E.157.175; 2.E.157.240; 2.E.157.244; 2.E.166.228; 2.E.166.229; 2.E.166.230; 2.E.166.231; 2.E.166.236; 2.E.166.237; 2.E.166.238; 2.E.166.239; 2.E.166.154; 2.E.166.157; 2.E.166.166; 2.E.166.169; 2.E.166.172; 2.E.166.175; 2.E.166.240; 2.E.166.244; 2.E.169.228; 2.E.169.229; 2.E.169.230; 2.E.169.231; 2.E.169.236; 2.E.169.237; 2.E.169.238; 2.E.169.239; 2.E.169.154; 2.E.169.157; 2.E.169.166; 2.E.169.169; 2.E.169.172; 2.E.169.175; 2.E.169.240;

2.E.169.244; 2.E.172.228; 2.E.172.229; 2.E.172.230; 2.E.172.231; 2.E.172.236; 2.E.172.237; 2.E.172.238; 2.E.172.239; 2.E.172.154; 2.E.172.157; 2.E.172.166; 2.E.172.169; 2.E.172.172; 2.E.172.175; 2.E.172.240; 2.E.172.244; 2.E.175.228; 2.E.175.229; 2.E.175.230; 2.E.175.231; 2.E.175.236; 2.E.175.237; 2.E.175.238; 2.E.175.239; 2.E.175.154; 2.E.175.157; 2.E.175.166; 2.E.175.169; 2.E.175.172; 2.E.175.175; 2.E.175.240; 2.E.175.244; 2.E.240.228; 2.E.240.229; 2.E.240.230; 2.E.240.231; 2.E.240.236; 2.E.240.237; 2.E.240.238; 2.E.240.239; 2.E.240.154; 2.E.240.157; 2.E.240.166; 2.E.240.169; 2.E.240.172; 2.E.240.175; 2.E.240.240; 2.E.240.244; 2.E.244.228; 2.E.244.229; 2.E.244.230; 2.E.244.231; 2.E.244.236; 2.E.244.237; 2.E.244.238; 2.E.244.239; 2.E.244.154; 2.E.244.157; 2.E.244.166; 2.E.244.169; 2.E.244.172; 2.E.244.175; 2.E.244.240; 2.E.244.244;

Prodrugs of 2.G

2.G.228.228; 2.G.228.229; 2.G.228.230; 2.G.228.231; 2.G.228.236; 2.G.228.237; 2.G.228.238; 2.G.228.239; 2.G.228.154; 2.G.228.157; 2.G.228.166; 2.G.228.169; 2.G.228.172; 2.G.228.175; 2.G.228.240; 2.G.228.244; 2.G.229.228; 2.G.229.229; 2.G.229.230; 2.G.229.231; 2.G.229.236; 2.G.229.237; 2.G.229.238; 2.G.229.239; 2.G.229.154; 2.G.229.157; 2.G.229.166; 2.G.229.169; 2.G.229.172; 2.G.229.175; 2.G.229.240; 2.G.229.244; 2.G.230.228; 2.G.230.229; 2.G.230.230; 2.G.230.231; 2.G.230.236; 2.G.230.237; 2.G.230.238; 2.G.230.239; 2.G.230.154; 2.G.230.157; 2.G.230.166; 2.G.230.169; 2.G.230.172; 2.G.230.175; 2.G.230.240; 2.G.230.244; 2.G.231.228; 2.G.231.229; 2.G.231.230; 2.G.231.231; 2.G.231.236; 2.G.231.237; 2.G.231.238; 2.G.231.239; 2.G.231.154; 2.G.231.157; 2.G.231.166; 2.G.231.169; 2.G.231.172; 2.G.231.175; 2.G.231.240; 2.G.231.244; 2.G.236.228; 2.G.236.229; 2.G.236.230; 2.G.236.231; 2.G.236.236; 2.G.236.237; 2.G.236.238; 2.G.236.239; 2.G.236.154; 2.G.236.157; 2.G.236.166; 2.G.236.169; 2.G.236.172; 2.G.236.175; 2.G.236.240; 2.G.236.244; 2.G.237.228; 2.G.237.229; 2.G.237.230; 2.G.237.231; 2.G.237.236;

2.G.237.237; 2.G.237.238; 2.G.237.239; 2.G.237.154; 2.G.237.157; 2.G.237.166; 2.G.237.169; 2.G.237.172; 2.G.237.175; 2.G.237.240; 2.G.237.244; 2.G.238.228; 2.G.238.229; 2.G.238.230; 2.G.238.231; 2.G.238.236; 2.G.238.237; 2.G.238.238; 2.G.238.239; 2.G.238.154; 2.G.238.157; 2.G.238.166; 2.G.238.169; 2.G.238.172; 2.G.238.175; 2.G.238.240; 2.G.238.244; 2.G.239.228; 2.G.239.229; 2.G.239.230; 2.G.239.231; 2.G.239.236; 2.G.239.237; 2.G.239.238; 2.G.239.239; 2.G.239.154; 2.G.239.157; 2.G.239.166; 2.G.239.169; 2.G.239.172; 2.G.239.175; 2.G.239.240; 2.G.239.244; 2.G.154.228; 2.G.154.229; 2.G.154.230; 2.G.154.231; 2.G.154.236; 2.G.154.237; 2.G.154.238; 2.G.154.239; 2.G.154.154; 2.G.154.157; 2.G.154.166; 2.G.154.169; 2.G.154.172; 2.G.154.175; 2.G.154.240; 2.G.154.244; 2.G.157.228; 2.G.157.229; 2.G.157.230; 2.G.157.231; 2.G.157.236; 2.G.157.237; 2.G.157.238; 2.G.157.239; 2.G.157.154; 2.G.157.157; 2.G.157.166; 2.G.157.169; 2.G.157.172; 2.G.157.175; 2.G.157.240; 2.G.157.244; 2.G.166.228; 2.G.166.229; 2.G.166.230; 2.G.166.231; 2.G.166.236; 2.G.166.237; 2.G.166.238; 2.G.166.239; 2.G.166.154; 2.G.166.157; 2.G.166.166; 2.G.166.169; 2.G.166.172; 2.G.166.175; 2.G.166.240; 2.G.166.244; 2.G.169.228; 2.G.169.229; 2.G.169.230; 2.G.169.231; 2.G.169.236; 2.G.169.237; 2.G.169.238; 2.G.169.239; 2.G.169.154; 2.G.169.157; 2.G.169.166; 2.G.169.169; 2.G.169.172; 2.G.169.175; 2.G.169.240; 2.G.169.244; 2.G.172.228; 2.G.172.229; 2.G.172.230; 2.G.172.231; 2.G.172.236; 2.G.172.237; 2.G.172.238; 2.G.172.239; 2.G.172.154; 2.G.172.157; 2.G.172.166; 2.G.172.169; 2.G.172.172; 2.G.172.175; 2.G.172.240; 2.G.172.244; 2.G.175.228; 2.G.175.229; 2.G.175.230; 2.G.175.231; 2.G.175.236; 2.G.175.237; 2.G.175.238; 2.G.175.239; 2.G.175.154; 2.G.175.157; 2.G.175.166; 2.G.175.169; 2.G.175.172; 2.G.175.175; 2.G.175.240; 2.G.175.244; 2.G.240.228; 2.G.240.229; 2.G.240.230; 2.G.240.231; 2.G.240.236; 2.G.240.237; 2.G.240.238; 2.G.240.239; 2.G.240.154; 2.G.240.157; 2.G.240.166;

2.G.240.169; 2.G.240.172; 2.G.240.175; 2.G.240.240; 2.G.240.244; 2.G.244.228; 2.G.244.229; 2.G.244.230; 2.G.244.231; 2.G.244.236; 2.G.244.237; 2.G.244.238; 2.G.244.239; 2.G.244.154; 2.G.244.157; 2.G.244.166; 2.G.244.169; 2.G.244.172; 2.G.244.175; 2.G.244.240; 2.G.244.244;

Prodrugs of 2.I

2.I.228.228; 2.I.228.229; 2.I.228.230; 2.I.228.231; 2.I.228.236; 2.I.228.237; 2.I.228.238; 2.I.228.239; 2.I.228.154; 2.I.228.157; 2.I.228.166; 2.I.228.169; 2.I.228.172; 2.I.228.175; 2.I.228.240; 2.I.228.244; 2.I.229.228; 2.I.229.229; 2.I.229.230; 2.I.229.231; 2.I.229.236; 2.I.229.237; 2.I.229.238; 2.I.229.239; 2.I.229.154; 2.I.229.157; 2.I.229.166; 2.I.229.169; 2.I.229.172; 2.I.229.175; 2.I.229.240; 2.I.229.244; 2.I.230.228; 2.I.230.229; 2.I.230.230; 2.I.230.231; 2.I.230.236; 2.I.230.237; 2.I.230.238; 2.I.230.239; 2.I.230.154; 2.I.230.157; 2.I.230.166; 2.I.230.169; 2.I.230.172; 2.I.230.175; 2.I.230.240; 2.I.230.244; 2.I.231.228; 2.I.231.229; 2.I.231.230; 2.I.231.231; 2.I.231.236; 2.I.231.237; 2.I.231.238; 2.I.231.239; 2.I.231.154; 2.I.231.157; 2.I.231.166; 2.I.231.169; 2.I.231.172; 2.I.231.175; 2.I.231.240; 2.I.231.244; 2.I.236.228; 2.I.236.229; 2.I.236.230; 2.I.236.231; 2.I.236.236; 2.I.236.237; 2.I.236.238; 2.I.236.239; 2.I.236.154; 2.I.236.157; 2.I.236.166; 2.I.236.169; 2.I.236.172; 2.I.236.175; 2.I.236.240; 2.I.236.244; 2.I.237.228; 2.I.237.229; 2.I.237.230; 2.I.237.231; 2.I.237.236; 2.I.237.237; 2.I.237.238; 2.I.237.239; 2.I.237.154; 2.I.237.157; 2.I.237.166; 2.I.237.169; 2.I.237.172; 2.I.237.175; 2.I.237.240; 2.I.237.244; 2.I.238.228; 2.I.238.229; 2.I.238.230; 2.I.238.231; 2.I.238.236; 2.I.238.237; 2.I.238.238; 2.I.238.239; 2.I.238.154; 2.I.238.157; 2.I.238.166; 2.I.238.169; 2.I.238.172; 2.I.238.175; 2.I.238.240; 2.I.238.244; 2.I.239.228; 2.I.239.229; 2.I.239.230; 2.I.239.231; 2.I.239.236; 2.I.239.237; 2.I.239.238; 2.I.239.239; 2.I.239.154; 2.I.239.157; 2.I.239.166; 2.I.239.169; 2.I.239.172; 2.I.239.175; 2.I.239.240; 2.I.239.244; 2.I.154.228; 2.I.154.229; 2.I.154.230; 2.I.154.231; 2.I.154.236; 2.I.154.237; 2.I.154.238; 2.I.154.239; 2.I.154.154; 2.I.154.157;

2.I.154.166; 2.I.154.169; 2.I.154.172; 2.I.154.175; 2.I.154.240; 2.I.154.244; 2.I.157.228; 2.I.157.229; 2.I.157.230; 2.I.157.231; 2.I.157.236; 2.I.157.237; 2.I.157.238; 2.I.157.239; 2.I.157.154; 2.I.157.157; 2.I.157.166; 2.I.157.169; 2.I.157.172; 2.I.157.175; 2.I.157.240; 2.I.157.244; 2.I.166.228; 2.I.166.229; 2.I.166.230; 2.I.166.231; 2.I.166.236; 2.I.166.237; 2.I.166.238; 2.I.166.239; 2.I.166.154; 2.I.166.157; 2.I.166.166; 2.I.166.169; 2.I.166.172; 2.I.166.175; 2.I.166.240; 2.I.166.244; 2.I.169.228; 2.I.169.229; 2.I.169.230; 2.I.169.231; 2.I.169.236; 2.I.169.237; 2.I.169.238; 2.I.169.239; 2.I.169.154; 2.I.169.157; 2.I.169.166; 2.I.169.169; 2.I.169.172; 2.I.169.175; 2.I.169.240; 2.I.169.244; 2.I.172.228; 2.I.172.229; 2.I.172.230; 2.I.172.231; 2.I.172.236; 2.I.172.237; 2.I.172.238; 2.I.172.239; 2.I.172.154; 2.I.172.157; 2.I.172.166; 2.I.172.169; 2.I.172.172; 2.I.172.175; 2.I.172.240; 2.I.172.244; 2.I.175.228; 2.I.175.229; 2.I.175.230; 2.I.175.231; 2.I.175.236; 2.I.175.237; 2.I.175.238; 2.I.175.239; 2.I.175.154; 2.I.175.157; 2.I.175.166; 2.I.175.169; 2.I.175.172; 2.I.175.175; 2.I.175.240; 2.I.175.244; 2.I.240.228; 2.I.240.229; 2.I.240.230; 2.I.240.231; 2.I.240.236; 2.I.240.237; 2.I.240.238; 2.I.240.239; 2.I.240.154; 2.I.240.157; 2.I.240.166; 2.I.240.169; 2.I.240.172; 2.I.240.175; 2.I.240.240; 2.I.240.244; 2.I.244.228; 2.I.244.229; 2.I.244.230; 2.I.244.231; 2.I.244.236; 2.I.244.237; 2.I.244.238; 2.I.244.239; 2.I.244.154; 2.I.244.157; 2.I.244.166; 2.I.244.169; 2.I.244.172; 2.I.244.175; 2.I.244.240; 2.I.244.244;

Prodrugs of 2.J

2.J.228.228; 2.J.228.229; 2.J.228.230; 2.J.228.231; 2.J.228.236; 2.J.228.237; 2.J.228.238; 2.J.228.239; 2.J.228.154; 2.J.228.157; 2.J.228.166; 2.J.228.169; 2.J.228.172; 2.J.228.175; 2.J.228.240; 2.J.228.244; 2.J.229.228; 2.J.229.229; 2.J.229.230; 2.J.229.231; 2.J.229.236; 2.J.229.237; 2.J.229.238; 2.J.229.239; 2.J.229.154; 2.J.229.157; 2.J.229.166; 2.J.229.169; 2.J.229.172; 2.J.229.175; 2.J.229.240; 2.J.229.244; 2.J.230.228; 2.J.230.229; 2.J.230.230; 2.J.230.231; 2.J.230.236; 2.J.230.237; 2.J.230.238; 2.J.230.239; 2.J.230.154; 2.J.230.157; 2.J.230.166; 2.J.230.169; 2.J.230.172; 2.J.230.175; 2.J.230.240; 2.J.230.244;

2.J.231.228; 2.J.231.229; 2.J.231.230; 2.J.231.231; 2.J.231.236; 2.J.231.237; 2.J.231.238; 2.J.231.239; 2.J.231.154; 2.J.231.157; 2.J.231.166; 2.J.231.169; 2.J.231.172; 2.J.231.175; 2.J.231.240; 2.J.231.244; 2.J.236.228; 2.J.236.229; 2.J.236.230; 2.J.236.231; 2.J.236.236; 2.J.236.237; 2.J.236.238; 2.J.236.239; 2.J.236.154; 2.J.236.157; 2.J.236.166; 2.J.236.169; 2.J.236.172; 2.J.236.175; 2.J.236.240; 2.J.236.244; 2.J.237.228; 2.J.237.229; 2.J.237.230; 2.J.237.231; 2.J.237.236; 2.J.237.237; 2.J.237.238; 2.J.237.239; 2.J.237.154; 2.J.237.157; 2.J.237.166; 2.J.237.169; 2.J.237.172; 2.J.237.175; 2.J.237.240; 2.J.237.244; 2.J.238.228; 2.J.238.229; 2.J.238.230; 2.J.238.231; 2.J.238.236; 2.J.238.237; 2.J.238.238; 2.J.238.239; 2.J.238.154; 2.J.238.157; 2.J.238.166; 2.J.238.169; 2.J.238.172; 2.J.238.175; 2.J.238.240; 2.J.238.244; 2.J.239.228; 2.J.239.229; 2.J.239.230; 2.J.239.231; 2.J.239.236; 2.J.239.237; 2.J.239.238; 2.J.239.239; 2.J.239.154; 2.J.239.157; 2.J.239.166; 2.J.239.169; 2.J.239.172; 2.J.239.175; 2.J.239.240; 2.J.239.244; 2.J.154.228; 2.J.154.229; 2.J.154.230; 2.J.154.231; 2.J.154.236; 2.J.154.237; 2.J.154.238; 2.J.154.239; 2.J.154.154; 2.J.154.157; 2.J.154.166; 2.J.154.169; 2.J.154.172; 2.J.154.175; 2.J.154.240; 2.J.154.244; 2.J.157.228; 2.J.157.229; 2.J.157.230; 2.J.157.231; 2.J.157.236; 2.J.157.237; 2.J.157.238; 2.J.157.239; 2.J.157.154; 2.J.157.157; 2.J.157.166; 2.J.157.169; 2.J.157.172; 2.J.157.175; 2.J.157.240; 2.J.157.244; 2.J.166.228; 2.J.166.229; 2.J.166.230; 2.J.166.231; 2.J.166.236; 2.J.166.237; 2.J.166.238; 2.J.166.239; 2.J.166.154; 2.J.166.157; 2.J.166.166; 2.J.166.169; 2.J.166.172; 2.J.166.175; 2.J.166.240; 2.J.166.244; 2.J.169.228; 2.J.169.229; 2.J.169.230; 2.J.169.231; 2.J.169.236; 2.J.169.237; 2.J.169.238; 2.J.169.239; 2.J.169.154; 2.J.169.157; 2.J.169.166; 2.J.169.169; 2.J.169.172; 2.J.169.175; 2.J.169.240; 2.J.169.244; 2.J.172.228; 2.J.172.229; 2.J.172.230; 2.J.172.231; 2.J.172.236; 2.J.172.237; 2.J.172.238; 2.J.172.239; 2.J.172.154; 2.J.172.157; 2.J.172.166; 2.J.172.169; 2.J.172.172; 2.J.172.175; 2.J.172.240; 2.J.172.244; 2.J.175.228; 2.J.175.229; 2.J.175.230; 2.J.175.231; 2.J.175.236; 2.J.175.237; 2.J.175.238; 2.J.175.239; 2.J.175.154; 2.J.175.157; 2.J.175.166; 2.J.175.169; 2.J.175.172; 2.J.175.175; 2.J.175.240; 2.J.175.244; 2.J.240.228; 2.J.240.229; 2.J.240.230; 2.J.240.231;

2.J.240.236; 2.J.240.237; 2.J.240.238; 2.J.240.239; 2.J.240.154; 2.J.240.157; 2.J.240.166; 2.J.240.169; 2.J.240.172; 2.J.240.175; 2.J.240.240; 2.J.240.244; 2.J.244.228; 2.J.244.229; 2.J.244.230; 2.J.244.231; 2.J.244.236; 2.J.244.237; 2.J.244.238; 2.J.244.239; 2.J.244.154; 2.J.244.157; 2.J.244.166; 2.J.244.169; 2.J.244.172; 2.J.244.175; 2.J.244.240; 2.J.244.244;

Prodrugs of 2.L

2.L.228.228; 2.L.228.229; 2.L.228.230; 2.L.228.231; 2.L.228.236; 2.L.228.237; 2.L.228.238; 2.L.228.239; 2.L.228.154; 2.L.228.157; 2.L.228.166; 2.L.228.169; 2.L.228.172; 2.L.228.175; 2.L.228.240; 2.L.228.244; 2.L.229.228; 2.L.229.229; 2.L.229.230; 2.L.229.231; 2.L.229.236; 2.L.229.237; 2.L.229.238; 2.L.229.239; 2.L.229.154; 2.L.229.157; 2.L.229.166; 2.L.229.169; 2.L.229.172; 2.L.229.175; 2.L.229.240; 2.L.229.244; 2.L.230.228; 2.L.230.229; 2.L.230.230; 2.L.230.231; 2.L.230.236; 2.L.230.237; 2.L.230.238; 2.L.230.239; 2.L.230.154; 2.L.230.157; 2.L.230.166; 2.L.230.169; 2.L.230.172; 2.L.230.175; 2.L.230.240; 2.L.230.244; 2.L.231.228; 2.L.231.229; 2.L.231.230; 2.L.231.231; 2.L.231.236; 2.L.231.237; 2.L.231.238; 2.L.231.239; 2.L.231.154; 2.L.231.157; 2.L.231.166; 2.L.231.169; 2.L.231.172; 2.L.231.175; 2.L.231.240; 2.L.231.244; 2.L.236.228; 2.L.236.229; 2.L.236.230; 2.L.236.231; 2.L.236.236; 2.L.236.237; 2.L.236.238; 2.L.236.239; 2.L.236.154; 2.L.236.157; 2.L.236.166; 2.L.236.169; 2.L.236.172; 2.L.236.175; 2.L.236.240; 2.L.236.244; 2.L.237.228; 2.L.237.229; 2.L.237.230; 2.L.237.231; 2.L.237.236; 2.L.237.237; 2.L.237.238; 2.L.237.239; 2.L.237.154; 2.L.237.157; 2.L.237.166; 2.L.237.169; 2.L.237.172; 2.L.237.175; 2.L.237.240; 2.L.237.244; 2.L.238.228; 2.L.238.229; 2.L.238.230; 2.L.238.231; 2.L.238.236; 2.L.238.237; 2.L.238.238; 2.L.238.239; 2.L.238.154; 2.L.238.157; 2.L.238.166; 2.L.238.169; 2.L.238.172; 2.L.238.175; 2.L.238.240; 2.L.238.244; 2.L.239.228; 2.L.239.229; 2.L.239.230; 2.L.239.231; 2.L.239.236; 2.L.239.237; 2.L.239.238; 2.L.239.239; 2.L.239.154; 2.L.239.157; 2.L.239.166; 2.L.239.169; 2.L.239.172; 2.L.239.175; 2.L.239.240; 2.L.239.244; 2.L.154.228; 2.L.154.229; 2.L.154.230; 2.L.154.231; 2.L.154.236; 2.L.154.237; 2.L.154.238; 2.L.154.239; 2.L.154.154;

2.L.154.157; 2.L.154.166; 2.L.154.169; 2.L.154.172; 2.L.154.175; 2.L.154.240; 2.L.154.244; 2.L.157.228; 2.L.157.229; 2.L.157.230; 2.L.157.231; 2.L.157.236; 2.L.157.237; 2.L.157.238; 2.L.157.239; 2.L.157.154; 2.L.157.157; 2.L.157.166; 2.L.157.169; 2.L.157.172; 2.L.157.175; 2.L.157.240; 2.L.157.244; 2.L.166.228; 2.L.166.229; 2.L.166.230; 2.L.166.231; 2.L.166.236; 2.L.166.237; 2.L.166.238; 2.L.166.239; 2.L.166.154; 2.L.166.157; 2.L.166.166; 2.L.166.169; 2.L.166.172; 2.L.166.175; 2.L.166.240; 2.L.166.244; 2.L.169.228; 2.L.169.229; 2.L.169.230; 2.L.169.231; 2.L.169.236; 2.L.169.237; 2.L.169.238; 2.L.169.239; 2.L.169.154; 2.L.169.157; 2.L.169.166; 2.L.169.169; 2.L.169.172; 2.L.169.175; 2.L.169.240; 2.L.169.244; 2.L.172.228; 2.L.172.229; 2.L.172.230; 2.L.172.231; 2.L.172.236; 2.L.172.237; 2.L.172.238; 2.L.172.239; 2.L.172.154; 2.L.172.157; 2.L.172.166; 2.L.172.169; 2.L.172.172; 2.L.172.175; 2.L.172.240; 2.L.172.244; 2.L.175.228; 2.L.175.229; 2.L.175.230; 2.L.175.231; 2.L.175.236; 2.L.175.237; 2.L.175.238; 2.L.175.239; 2.L.175.154; 2.L.175.157; 2.L.175.166; 2.L.175.169; 2.L.175.172; 2.L.175.175; 2.L.175.240; 2.L.175.244; 2.L.240.228; 2.L.240.229; 2.L.240.230; 2.L.240.231; 2.L.240.236; 2.L.240.237; 2.L.240.238; 2.L.240.239; 2.L.240.154; 2.L.240.157; 2.L.240.166; 2.L.240.169; 2.L.240.172; 2.L.240.175; 2.L.240.240; 2.L.240.244; 2.L.244.228; 2.L.244.229; 2.L.244.230; 2.L.244.231; 2.L.244.236; 2.L.244.237; 2.L.244.238; 2.L.244.239; 2.L.244.154; 2.L.244.157; 2.L.244.166; 2.L.244.169; 2.L.244.172; 2.L.244.175; 2.L.244.240; 2.L.244.244;

Prodrugs of 2.O

2.O.228.228; 2.O.228.229; 2.O.228.230; 2.O.228.231; 2.O.228.236; 2.O.228.237; 2.O.228.238; 2.O.228.239; 2.O.228.154; 2.O.228.157; 2.O.228.166; 2.O.228.169; 2.O.228.172; 2.O.228.175; 2.O.228.240; 2.O.228.244; 2.O.229.228; 2.O.229.229; 2.O.229.230; 2.O.229.231; 2.O.229.236; 2.O.229.237; 2.O.229.238; 2.O.229.239; 2.O.229.154; 2.O.229.157; 2.O.229.166; 2.O.229.169; 2.O.229.172; 2.O.229.175; 2.O.229.240; 2.O.229.244; 2.O.230.228; 2.O.230.229; 2.O.230.230; 2.O.230.231; 2.O.230.236; 2.O.230.237; 2.O.230.238; 2.O.230.239;

2.O.230.154; 2.O.230.157; 2.O.230.166; 2.O.230.169; 2.O.230.172; 2.O.230.175; 2.O.230.240; 2.O.230.244; 2.O.231.228; 2.O.231.229; 2.O.231.230; 2.O.231.231; 2.O.231.236; 2.O.231.237; 2.O.231.238; 2.O.231.239; 2.O.231.154; 2.O.231.157; 2.O.231.166; 2.O.231.169; 2.O.231.172; 2.O.231.175; 2.O.231.240; 2.O.231.244; 2.O.236.228; 2.O.236.229; 2.O.236.230; 2.O.236.231; 2.O.236.236; 2.O.236.237; 2.O.236.238; 2.O.236.239; 2.O.236.154; 2.O.236.157; 2.O.236.166; 2.O.236.169; 2.O.236.172; 2.O.236.175; 2.O.236.240; 2.O.236.244; 2.O.237.228; 2.O.237.229; 2.O.237.230; 2.O.237.231; 2.O.237.236; 2.O.237.237; 2.O.237.238; 2.O.237.239; 2.O.237.154; 2.O.237.157; 2.O.237.166; 2.O.237.169; 2.O.237.172; 2.O.237.175; 2.O.237.240; 2.O.237.244; 2.O.238.228; 2.O.238.229; 2.O.238.230; 2.O.238.231; 2.O.238.236; 2.O.238.237; 2.O.238.238; 2.O.238.239; 2.O.238.154; 2.O.238.157; 2.O.238.166; 2.O.238.169; 2.O.238.172; 2.O.238.175; 2.O.238.240; 2.O.238.244; 2.O.239.228; 2.O.239.229; 2.O.239.230; 2.O.239.231; 2.O.239.236; 2.O.239.237; 2.O.239.238; 2.O.239.239; 2.O.239.154; 2.O.239.157; 2.O.239.166; 2.O.239.169; 2.O.239.172; 2.O.239.175; 2.O.239.240; 2.O.239.244; 2.O.154.228; 2.O.154.229; 2.O.154.230; 2.O.154.231; 2.O.154.236; 2.O.154.237; 2.O.154.238; 2.O.154.239; 2.O.154.154; 2.O.154.157; 2.O.154.166; 2.O.154.169; 2.O.154.172; 2.O.154.175; 2.O.154.240; 2.O.154.244; 2.O.157.228; 2.O.157.229; 2.O.157.230; 2.O.157.231; 2.O.157.236; 2.O.157.237; 2.O.157.238; 2.O.157.239; 2.O.157.154; 2.O.157.157; 2.O.157.166; 2.O.157.169; 2.O.157.172; 2.O.157.175; 2.O.157.240; 2.O.157.244; 2.O.166.228; 2.O.166.229; 2.O.166.230; 2.O.166.231; 2.O.166.236; 2.O.166.237; 2.O.166.238; 2.O.166.239; 2.O.166.154; 2.O.166.157; 2.O.166.166; 2.O.166.169; 2.O.166.172; 2.O.166.175; 2.O.166.240; 2.O.166.244; 2.O.169.228; 2.O.169.229; 2.O.169.230; 2.O.169.231; 2.O.169.236; 2.O.169.237; 2.O.169.238; 2.O.169.239; 2.O.169.154; 2.O.169.157; 2.O.169.166; 2.O.169.169; 2.O.169.172; 2.O.169.175;

2.O.169.240; 2.O.169.244; 2.O.172.228; 2.O.172.229; 2.O.172.230; 2.O.172.231; 2.O.172.236; 2.O.172.237; 2.O.172.238; 2.O.172.239; 2.O.172.154; 2.O.172.157; 2.O.172.166; 2.O.172.169; 2.O.172.172; 2.O.172.175; 2.O.172.240; 2.O.172.244; 2.O.175.228; 2.O.175.229; 2.O.175.230; 2.O.175.231; 2.O.175.236; 2.O.175.237; 2.O.175.238; 2.O.175.239; 2.O.175.154; 2.O.175.157; 2.O.175.166; 2.O.175.169; 2.O.175.172; 2.O.175.175; 2.O.175.240; 2.O.175.244; 2.O.240.228; 2.O.240.229; 2.O.240.230; 2.O.240.231; 2.O.240.236; 2.O.240.237; 2.O.240.238; 2.O.240.239; 2.O.240.154; 2.O.240.157; 2.O.240.166; 2.O.240.169; 2.O.240.172; 2.O.240.175; 2.O.240.240; 2.O.240.244; 2.O.244.228; 2.O.244.229; 2.O.244.230; 2.O.244.231; 2.O.244.236; 2.O.244.237; 2.O.244.238; 2.O.244.239; 2.O.244.154; 2.O.244.157; 2.O.244.166; 2.O.244.169; 2.O.244.172; 2.O.244.175; 2.O.244.240; 2.O.244.244;

Prodrugs of 2.P

2.P.228.228; 2.P.228.229; 2.P.228.230; 2.P.228.231; 2.P.228.236; 2.P.228.237; 2.P.228.238; 2.P.228.239; 2.P.228.154; 2.P.228.157; 2.P.228.166; 2.P.228.169; 2.P.228.172; 2.P.228.175; 2.P.228.240; 2.P.228.244; 2.P.229.228; 2.P.229.229; 2.P.229.230; 2.P.229.231; 2.P.229.236; 2.P.229.237; 2.P.229.238; 2.P.229.239; 2.P.229.154; 2.P.229.157; 2.P.229.166; 2.P.229.169; 2.P.229.172; 2.P.229.175; 2.P.229.240; 2.P.229.244; 2.P.230.228; 2.P.230.229; 2.P.230.230; 2.P.230.231; 2.P.230.236; 2.P.230.237; 2.P.230.238; 2.P.230.239; 2.P.230.154; 2.P.230.157; 2.P.230.166; 2.P.230.169; 2.P.230.172; 2.P.230.175; 2.P.230.240; 2.P.230.244; 2.P.231.228; 2.P.231.229; 2.P.231.230; 2.P.231.231; 2.P.231.236; 2.P.231.237; 2.P.231.238; 2.P.231.239; 2.P.231.154; 2.P.231.157; 2.P.231.166; 2.P.231.169; 2.P.231.172; 2.P.231.175; 2.P.231.240; 2.P.231.244; 2.P.236.228; 2.P.236.229; 2.P.236.230; 2.P.236.231; 2.P.236.236; 2.P.236.237; 2.P.236.238; 2.P.236.239; 2.P.236.154; 2.P.236.157; 2.P.236.166; 2.P.236.169; 2.P.236.172; 2.P.236.175; 2.P.236.240; 2.P.236.244; 2.P.237.228; 2.P.237.229; 2.P.237.230;

2.P.237.231; 2.P.237.236; 2.P.237.237; 2.P.237.238; 2.P.237.239; 2.P.237.154; 2.P.237.157; 2.P.237.166; 2.P.237.169; 2.P.237.172; 2.P.237.175; 2.P.237.240; 2.P.237.244; 2.P.238.228; 2.P.238.229; 2.P.238.230; 2.P.238.231; 2.P.238.236; 2.P.238.237; 2.P.238.238; 2.P.238.239; 2.P.238.154; 2.P.238.157; 2.P.238.166; 2.P.238.169; 2.P.238.172; 2.P.238.175; 2.P.238.240; 2.P.238.244; 2.P.239.228; 2.P.239.229; 2.P.239.230; 2.P.239.231; 2.P.239.236; 2.P.239.237; 2.P.239.238; 2.P.239.239; 2.P.239.154; 2.P.239.157; 2.P.239.166; 2.P.239.169; 2.P.239.172; 2.P.239.175; 2.P.239.240; 2.P.239.244; 2.P.154.228; 2.P.154.229; 2.P.154.230; 2.P.154.231; 2.P.154.236; 2.P.154.237; 2.P.154.238; 2.P.154.239; 2.P.154.154; 2.P.154.157; 2.P.154.166; 2.P.154.169; 2.P.154.172; 2.P.154.175; 2.P.154.240; 2.P.154.244; 2.P.157.228; 2.P.157.229; 2.P.157.230; 2.P.157.231; 2.P.157.236; 2.P.157.237; 2.P.157.238; 2.P.157.239; 2.P.157.154; 2.P.157.157; 2.P.157.166; 2.P.157.169; 2.P.157.172; 2.P.157.175; 2.P.157.240; 2.P.157.244; 2.P.166.228; 2.P.166.229; 2.P.166.230; 2.P.166.231; 2.P.166.236; 2.P.166.237; 2.P.166.238; 2.P.166.239; 2.P.166.154; 2.P.166.157; 2.P.166.166; 2.P.166.169; 2.P.166.172; 2.P.166.175; 2.P.166.240; 2.P.166.244; 2.P.169.228; 2.P.169.229; 2.P.169.230; 2.P.169.231; 2.P.169.236; 2.P.169.237; 2.P.169.238; 2.P.169.239; 2.P.169.154; 2.P.169.157; 2.P.169.166; 2.P.169.169; 2.P.169.172; 2.P.169.175; 2.P.169.240; 2.P.169.244; 2.P.172.228; 2.P.172.229; 2.P.172.230; 2.P.172.231; 2.P.172.236; 2.P.172.237; 2.P.172.238; 2.P.172.239; 2.P.172.154; 2.P.172.157; 2.P.172.166; 2.P.172.169; 2.P.172.172; 2.P.172.175; 2.P.172.240; 2.P.172.244; 2.P.175.228; 2.P.175.229; 2.P.175.230; 2.P.175.231; 2.P.175.236; 2.P.175.237; 2.P.175.238; 2.P.175.239; 2.P.175.154; 2.P.175.157; 2.P.175.166; 2.P.175.169; 2.P.175.172; 2.P.175.175; 2.P.175.240; 2.P.175.244; 2.P.240.228; 2.P.240.229; 2.P.240.230; 2.P.240.231; 2.P.240.236; 2.P.240.237; 2.P.240.238; 2.P.240.239; 2.P.240.154; 2.P.240.157; 2.P.240.166; 2.P.240.169; 2.P.240.172; 2.P.240.175; 2.P.240.240; 2.P.240.244; 2.P.244.228; 2.P.244.229; 2.P.244.230; 2.P.244.231; 2.P.244.236; 2.P.244.237; 2.P.244.238; 2.P.244.239; 2.P.244.154; 2.P.244.157; 2.P.244.166; 2.P.244.169; 2.P.244.172; 2.P.244.175; 2.P.244.240; 2.P.244.244;

Prodrugs of 2.U

2.U.228.228; 2.U.228.229; 2.U.228.230; 2.U.228.231; 2.U.228.236; 2.U.228.237; 2.U.228.238; 2.U.228.239; 2.U.228.154; 2.U.228.157; 2.U.228.166; 2.U.228.169; 2.U.228.172; 2.U.228.175; 2.U.228.240; 2.U.228.244; 2.U.229.228; 2.U.229.229; 2.U.229.230; 2.U.229.231; 2.U.229.236; 2.U.229.237; 2.U.229.238; 2.U.229.239; 2.U.229.154; 2.U.229.157; 2.U.229.166; 2.U.229.169; 2.U.229.172; 2.U.229.175; 2.U.229.240; 2.U.229.244; 2.U.230.228; 2.U.230.229; 2.U.230.230; 2.U.230.231; 2.U.230.236; 2.U.230.237; 2.U.230.238; 2.U.230.239; 2.U.230.154; 2.U.230.157; 2.U.230.166; 2.U.230.169; 2.U.230.172; 2.U.230.175; 2.U.230.240; 2.U.230.244; 2.U.231.228; 2.U.231.229; 2.U.231.230; 2.U.231.231; 2.U.231.236; 2.U.231.237; 2.U.231.238; 2.U.231.239; 2.U.231.154; 2.U.231.157; 2.U.231.166; 2.U.231.169; 2.U.231.172; 2.U.231.175; 2.U.231.240; 2.U.231.244; 2.U.236.228; 2.U.236.229; 2.U.236.230; 2.U.236.231; 2.U.236.236; 2.U.236.237; 2.U.236.238; 2.U.236.239; 2.U.236.154; 2.U.236.157; 2.U.236.166; 2.U.236.169; 2.U.236.172; 2.U.236.175; 2.U.236.240; 2.U.236.244; 2.U.237.228; 2.U.237.229; 2.U.237.230; 2.U.237.231; 2.U.237.236; 2.U.237.237; 2.U.237.238; 2.U.237.239; 2.U.237.154; 2.U.237.157; 2.U.237.166; 2.U.237.169; 2.U.237.172; 2.U.237.175; 2.U.237.240; 2.U.237.244; 2.U.238.228; 2.U.238.229; 2.U.238.230; 2.U.238.231; 2.U.238.236; 2.U.238.237; 2.U.238.238; 2.U.238.239; 2.U.238.154; 2.U.238.157; 2.U.238.166; 2.U.238.169; 2.U.238.172; 2.U.238.175; 2.U.238.240; 2.U.238.244; 2.U.239.228; 2.U.239.229; 2.U.239.230; 2.U.239.231; 2.U.239.236; 2.U.239.237; 2.U.239.238; 2.U.239.239; 2.U.239.154; 2.U.239.157; 2.U.239.166; 2.U.239.169; 2.U.239.172; 2.U.239.175; 2.U.239.240; 2.U.239.244; 2.U.154.228; 2.U.154.229; 2.U.154.230; 2.U.154.231; 2.U.154.236; 2.U.154.237; 2.U.154.238; 2.U.154.239; 2.U.154.154; 2.U.154.157; 2.U.154.166; 2.U.154.169; 2.U.154.172; 2.U.154.175; 2.U.154.240; 2.U.154.244; 2.U.157.228;

2.U.157.229; 2.U.157.230; 2.U.157.231; 2.U.157.236; 2.U.157.237; 2.U.157.238; 2.U.157.239; 2.U.157.154; 2.U.157.157; 2.U.157.166; 2.U.157.169; 2.U.157.172; 2.U.157.175; 2.U.157.240; 2.U.157.244; 2.U.166.228; 2.U.166.229; 2.U.166.230; 2.U.166.231; 2.U.166.236; 2.U.166.237; 2.U.166.238; 2.U.166.239; 2.U.166.154; 2.U.166.157; 2.U.166.166; 2.U.166.169; 2.U.166.172; 2.U.166.175; 2.U.166.240; 2.U.166.244; 2.U.169.228; 2.U.169.229; 2.U.169.230; 2.U.169.231; 2.U.169.236; 2.U.169.237; 2.U.169.238; 2.U.169.239; 2.U.169.154; 2.U.169.157; 2.U.169.166; 2.U.169.169; 2.U.169.172; 2.U.169.175; 2.U.169.240; 2.U.169.244; 2.U.172.228; 2.U.172.229; 2.U.172.230; 2.U.172.231; 2.U.172.236; 2.U.172.237; 2.U.172.238; 2.U.172.239; 2.U.172.154; 2.U.172.157; 2.U.172.166; 2.U.172.169; 2.U.172.172; 2.U.172.175; 2.U.172.240; 2.U.172.244; 2.U.175.228; 2.U.175.229; 2.U.175.230; 2.U.175.231; 2.U.175.236; 2.U.175.237; 2.U.175.238; 2.U.175.239; 2.U.175.154; 2.U.175.157; 2.U.175.166; 2.U.175.169; 2.U.175.172; 2.U.175.175; 2.U.175.240; 2.U.175.244; 2.U.240.228; 2.U.240.229; 2.U.240.230; 2.U.240.231; 2.U.240.236; 2.U.240.237; 2.U.240.238; 2.U.240.239; 2.U.240.154; 2.U.240.157; 2.U.240.166; 2.U.240.169; 2.U.240.172; 2.U.240.175; 2.U.240.240; 2.U.240.244; 2.U.244.228; 2.U.244.229; 2.U.244.230; 2.U.244.231; 2.U.244.236; 2.U.244.237; 2.U.244.238; 2.U.244.239; 2.U.244.154; 2.U.244.157; 2.U.244.166; 2.U.244.169; 2.U.244.172; 2.U.244.175; 2.U.244.240; 2.U.244.244;

Prodrugs of 2.W

2.W.228.228; 2.W.228.229; 2.W.228.230; 2.W.228.231; 2.W.228.236; 2.W.228.237; 2.W.228.238; 2.W.228.239; 2.W.228.154; 2.W.228.157; 2.W.228.166; 2.W.228.169; 2.W.228.172; 2.W.228.175; 2.W.228.240; 2.W.228.244; 2.W.229.228; 2.W.229.229; 2.W.229.230; 2.W.229.231; 2.W.229.236; 2.W.229.237; 2.W.229.238; 2.W.229.239; 2.W.229.154;

2.W.229.157; 2.W.229.166; 2.W.229.169; 2.W.229.172; 2.W.229.175; 2.W.229.240; 2.W.229.244; 2.W.230.228; 2.W.230.229; 2.W.230.230; 2.W.230.231; 2.W.230.236; 2.W.230.237; 2.W.230.238; 2.W.230.239; 2.W.230.154; 2.W.230.157; 2.W.230.166; 2.W.230.169; 2.W.230.172; 2.W.230.175; 2.W.230.240; 2.W.230.244; 2.W.231.228; 2.W.231.229; 2.W.231.230; 2.W.231.231; 2.W.231.236; 2.W.231.237; 2.W.231.238; 2.W.231.239; 2.W.231.154; 2.W.231.157; 2.W.231.166; 2.W.231.169; 2.W.231.172; 2.W.231.175; 2.W.231.240; 2.W.231.244; 2.W.236.228; 2.W.236.229; 2.W.236.230; 2.W.236.231; 2.W.236.236; 2.W.236.237; 2.W.236.238; 2.W.236.239; 2.W.236.154; 2.W.236.157; 2.W.236.166; 2.W.236.169; 2.W.236.172; 2.W.236.175; 2.W.236.240; 2.W.236.244; 2.W.237.228; 2.W.237.229; 2.W.237.230; 2.W.237.231; 2.W.237.236; 2.W.237.237; 2.W.237.238; 2.W.237.239; 2.W.237.154; 2.W.237.157; 2.W.237.166; 2.W.237.169; 2.W.237.172; 2.W.237.175; 2.W.237.240; 2.W.237.244; 2.W.238.228; 2.W.238.229; 2.W.238.230; 2.W.238.231; 2.W.238.236; 2.W.238.237; 2.W.238.238; 2.W.238.239; 2.W.238.154; 2.W.238.157; 2.W.238.166; 2.W.238.169; 2.W.238.172; 2.W.238.175; 2.W.238.240; 2.W.238.244; 2.W.239.228; 2.W.239.229; 2.W.239.230; 2.W.239.231; 2.W.239.236; 2.W.239.237; 2.W.239.238; 2.W.239.239; 2.W.239.154; 2.W.239.157; 2.W.239.166; 2.W.239.169; 2.W.239.172; 2.W.239.175; 2.W.239.240; 2.W.239.244; 2.W.154.228; 2.W.154.229; 2.W.154.230; 2.W.154.231; 2.W.154.236; 2.W.154.237; 2.W.154.238; 2.W.154.239; 2.W.154.154; 2.W.154.157; 2.W.154.166; 2.W.154.169; 2.W.154.172; 2.W.154.175; 2.W.154.240; 2.W.154.244; 2.W.157.228; 2.W.157.229; 2.W.157.230; 2.W.157.231; 2.W.157.236; 2.W.157.237; 2.W.157.238; 2.W.157.239; 2.W.157.154; 2.W.157.157; 2.W.157.166; 2.W.157.169; 2.W.157.172; 2.W.157.175; 2.W.157.240; 2.W.157.244; 2.W.166.228; 2.W.166.229; 2.W.166.230; 2.W.166.231; 2.W.166.236; 2.W.166.237; 2.W.166.238; 2.W.166.239; 2.W.166.154; 2.W.166.157; 2.W.166.166; 2.W.166.169; 2.W.166.172; 2.W.166.175; 2.W.166.240;

2.W.166.244; 2.W.169.228; 2.W.169.229; 2.W.169.230; 2.W.169.231; 2.W.169.236; 2.W.169.237; 2.W.169.238; 2.W.169.239; 2.W.169.154; 2.W.169.157; 2.W.169.166; 2.W.169.169; 2.W.169.172; 2.W.169.175; 2.W.169.240; 2.W.169.244; 2.W.172.228; 2.W.172.229; 2.W.172.230; 2.W.172.231; 2.W.172.236; 2.W.172.237; 2.W.172.238; 2.W.172.239; 2.W.172.154; 2.W.172.157; 2.W.172.166; 2.W.172.169; 2.W.172.172; 2.W.172.175; 2.W.172.240; 2.W.172.244; 2.W.175.228; 2.W.175.229; 2.W.175.230; 2.W.175.231; 2.W.175.236; 2.W.175.237; 2.W.175.238; 2.W.175.239; 2.W.175.154; 2.W.175.157; 2.W.175.166; 2.W.175.169; 2.W.175.172; 2.W.175.175; 2.W.175.240; 2.W.175.244; 2.W.240.228; 2.W.240.229; 2.W.240.230; 2.W.240.231; 2.W.240.236; 2.W.240.237; 2.W.240.238; 2.W.240.239; 2.W.240.154; 2.W.240.157; 2.W.240.166; 2.W.240.169; 2.W.240.172; 2.W.240.175; 2.W.240.240; 2.W.240.244; 2.W.244.228; 2.W.244.229; 2.W.244.230; 2.W.244.231; 2.W.244.236; 2.W.244.237; 2.W.244.238; 2.W.244.239; 2.W.244.154; 2.W.244.157; 2.W.244.166; 2.W.244.169; 2.W.244.172; 2.W.244.175; 2.W.244.240; 2.W.244.244;

Prodrugs of 2.Y

2.Y.228.228; 2.Y.228.229; 2.Y.228.230; 2.Y.228.231; 2.Y.228.236; 2.Y.228.237; 2.Y.228.238; 2.Y.228.239; 2.Y.228.154; 2.Y.228.157; 2.Y.228.166; 2.Y.228.169; 2.Y.228.172; 2.Y.228.175; 2.Y.228.240; 2.Y.228.244; 2.Y.229.228; 2.Y.229.229; 2.Y.229.230; 2.Y.229.231; 2.Y.229.236; 2.Y.229.237; 2.Y.229.238; 2.Y.229.239; 2.Y.229.154; 2.Y.229.157; 2.Y.229.166; 2.Y.229.169; 2.Y.229.172; 2.Y.229.175; 2.Y.229.240; 2.Y.229.244; 2.Y.230.228; 2.Y.230.229; 2.Y.230.230; 2.Y.230.231; 2.Y.230.236; 2.Y.230.237; 2.Y.230.238; 2.Y.230.239; 2.Y.230.154; 2.Y.230.157; 2.Y.230.166; 2.Y.230.169; 2.Y.230.172; 2.Y.230.175; 2.Y.230.240; 2.Y.230.244; 2.Y.231.228; 2.Y.231.229; 2.Y.231.230; 2.Y.231.231; 2.Y.231.236; 2.Y.231.237; 2.Y.231.238; 2.Y.231.239; 2.Y.231.154; 2.Y.231.157; 2.Y.231.166; 2.Y.231.169; 2.Y.231.172; 2.Y.231.175; 2.Y.231.240; 2.Y.231.244; 2.Y.236.228;

2.Y.236.229; 2.Y.236.230; 2.Y.236.231; 2.Y.236.236; 2.Y.236.237; 2.Y.236.238; 2.Y.236.239; 2.Y.236.154; 2.Y.236.157; 2.Y.236.166; 2.Y.236.169; 2.Y.236.172; 2.Y.236.175; 2.Y.236.240; 2.Y.236.244; 2.Y.237.228; 2.Y.237.229; 2.Y.237.230; 2.Y.237.231; 2.Y.237.236; 2.Y.237.237; 2.Y.237.238; 2.Y.237.239; 2.Y.237.154; 2.Y.237.157; 2.Y.237.166; 2.Y.237.169; 2.Y.237.172; 2.Y.237.175; 2.Y.237.240; 2.Y.237.244; 2.Y.238.228; 2.Y.238.229; 2.Y.238.230; 2.Y.238.231; 2.Y.238.236; 2.Y.238.237; 2.Y.238.238; 2.Y.238.239; 2.Y.238.154; 2.Y.238.157; 2.Y.238.166; 2.Y.238.169; 2.Y.238.172; 2.Y.238.175; 2.Y.238.240; 2.Y.238.244; 2.Y.239.228; 2.Y.239.229; 2.Y.239.230; 2.Y.239.231; 2.Y.239.236; 2.Y.239.237; 2.Y.239.238; 2.Y.239.239; 2.Y.239.154; 2.Y.239.157; 2.Y.239.166; 2.Y.239.169; 2.Y.239.172; 2.Y.239.175; 2.Y.239.240; 2.Y.239.244; 2.Y.154.228; 2.Y.154.229; 2.Y.154.230; 2.Y.154.231; 2.Y.154.236; 2.Y.154.237; 2.Y.154.238; 2.Y.154.239; 2.Y.154.154; 2.Y.154.157; 2.Y.154.166; 2.Y.154.169; 2.Y.154.172; 2.Y.154.175; 2.Y.154.240; 2.Y.154.244; 2.Y.157.228; 2.Y.157.229; 2.Y.157.230; 2.Y.157.231; 2.Y.157.236; 2.Y.157.237; 2.Y.157.238; 2.Y.157.239; 2.Y.157.154; 2.Y.157.157; 2.Y.157.166; 2.Y.157.169; 2.Y.157.172; 2.Y.157.175; 2.Y.157.240; 2.Y.157.244; 2.Y.166.228; 2.Y.166.229; 2.Y.166.230; 2.Y.166.231; 2.Y.166.236; 2.Y.166.237; 2.Y.166.238; 2.Y.166.239; 2.Y.166.154; 2.Y.166.157; 2.Y.166.166; 2.Y.166.169; 2.Y.166.172; 2.Y.166.175; 2.Y.166.240; 2.Y.166.244; 2.Y.169.228; 2.Y.169.229; 2.Y.169.230; 2.Y.169.231; 2.Y.169.236; 2.Y.169.237; 2.Y.169.238; 2.Y.169.239; 2.Y.169.154; 2.Y.169.157; 2.Y.169.166; 2.Y.169.169; 2.Y.169.172; 2.Y.169.175; 2.Y.169.240; 2.Y.169.244; 2.Y.172.228; 2.Y.172.229; 2.Y.172.230; 2.Y.172.231; 2.Y.172.236; 2.Y.172.237; 2.Y.172.238; 2.Y.172.239; 2.Y.172.154; 2.Y.172.157; 2.Y.172.166; 2.Y.172.169; 2.Y.172.172; 2.Y.172.175; 2.Y.172.240; 2.Y.172.244; 2.Y.175.228; 2.Y.175.229; 2.Y.175.230; 2.Y.175.231; 2.Y.175.236; 2.Y.175.237; 2.Y.175.238; 2.Y.175.239; 2.Y.175.154; 2.Y.175.157; 2.Y.175.166; 2.Y.175.169; 2.Y.175.172; 2.Y.175.175; 2.Y.175.240; 2.Y.175.244; 2.Y.240.228; 2.Y.240.229; 2.Y.240.230; 2.Y.240.231; 2.Y.240.236; 2.Y.240.237; 2.Y.240.238; 2.Y.240.239; 2.Y.240.154; 2.Y.240.157; 2.Y.240.166; 2.Y.240.169; 2.Y.240.172; 2.Y.240.175; 2.Y.240.240; 2.Y.240.244; 2.Y.244.228; 2.Y.244.229; 2.Y.244.230; 2.Y.244.231; 2.Y.244.236;

2.Y.244.237; 2.Y.244.238; 2.Y.244.239; 2.Y.244.154; 2.Y.244.157; 2.Y.244.166; 2.Y.244.169; 2.Y.244.172; 2.Y.244.175; 2.Y.244.240; 2.Y.244.244;

Prodrugs of 3.B

3.B.228.228; 3.B.228.229; 3.B.228.230; 3.B.228.231; 3.B.228.236; 3.B.228.237; 3.B.228.238; 3.B.228.239; 3.B.228.154; 3.B.228.157; 3.B.228.166; 3.B.228.169; 3.B.228.172; 3.B.228.175; 3.B.228.240; 3.B.228.244; 3.B.229.228; 3.B.229.229; 3.B.229.230; 3.B.229.231; 3.B.229.236; 3.B.229.237; 3.B.229.238; 3.B.229.239; 3.B.229.154; 3.B.229.157; 3.B.229.166; 3.B.229.169; 3.B.229.172; 3.B.229.175; 3.B.229.240; 3.B.229.244; 3.B.230.228; 3.B.230.229; 3.B.230.230; 3.B.230.231; 3.B.230.236; 3.B.230.237; 3.B.230.238; 3.B.230.239; 3.B.230.154; 3.B.230.157; 3.B.230.166; 3.B.230.169; 3.B.230.172; 3.B.230.175; 3.B.230.240; 3.B.230.244; 3.B.231.228; 3.B.231.229; 3.B.231.230; 3.B.231.231; 3.B.231.236; 3.B.231.237; 3.B.231.238; 3.B.231.239; 3.B.231.154; 3.B.231.157; 3.B.231.166; 3.B.231.169; 3.B.231.172; 3.B.231.175; 3.B.231.240; 3.B.231.244; 3.B.236.228; 3.B.236.229; 3.B.236.230; 3.B.236.231; 3.B.236.236; 3.B.236.237; 3.B.236.238; 3.B.236.239; 3.B.236.154; 3.B.236.157; 3.B.236.166; 3.B.236.169; 3.B.236.172; 3.B.236.175; 3.B.236.240; 3.B.236.244; 3.B.237.228; 3.B.237.229; 3.B.237.230; 3.B.237.231; 3.B.237.236; 3.B.237.237; 3.B.237.238; 3.B.237.239; 3.B.237.154; 3.B.237.157; 3.B.237.166; 3.B.237.169; 3.B.237.172; 3.B.237.175; 3.B.237.240; 3.B.237.244; 3.B.238.228; 3.B.238.229; 3.B.238.230; 3.B.238.231; 3.B.238.236; 3.B.238.237; 3.B.238.238; 3.B.238.239; 3.B.238.154; 3.B.238.157; 3.B.238.166; 3.B.238.169; 3.B.238.172; 3.B.238.175; 3.B.238.240; 3.B.238.244; 3.B.239.228; 3.B.239.229; 3.B.239.230; 3.B.239.231; 3.B.239.236; 3.B.239.237; 3.B.239.238; 3.B.239.239; 3.B.239.154; 3.B.239.157; 3.B.239.166; 3.B.239.169; 3.B.239.172; 3.B.239.175; 3.B.239.240; 3.B.239.244; 3.B.154.228; 3.B.154.229; 3.B.154.230; 3.B.154.231; 3.B.154.236; 3.B.154.237; 3.B.154.238; 3.B.154.239; 3.B.154.154; 3.B.154.157; 3.B.154.166; 3.B.154.169; 3.B.154.172; 3.B.154.175; 3.B.154.240; 3.B.154.244; 3.B.157.228; 3.B.157.229; 3.B.157.230; 3.B.157.231; 3.B.157.236; 3.B.157.237; 3.B.157.238; 3.B.157.239; 3.B.157.154; 3.B.157.157; 3.B.157.166;

3.B.157.169; 3.B.157.172; 3.B.157.175; 3.B.157.240; 3.B.157.244; 3.B.166.228; 3.B.166.229; 3.B.166.230; 3.B.166.231; 3.B.166.236; 3.B.166.237; 3.B.166.238; 3.B.166.239; 3.B.166.154; 3.B.166.157; 3.B.166.166; 3.B.166.169; 3.B.166.172; 3.B.166.175; 3.B.166.240; 3.B.166.244; 3.B.169.228; 3.B.169.229; 3.B.169.230; 3.B.169.231; 3.B.169.236; 3.B.169.237; 3.B.169.238; 3.B.169.239; 3.B.169.154; 3.B.169.157; 3.B.169.166; 3.B.169.169; 3.B.169.172; 3.B.169.175; 3.B.169.240; 3.B.169.244; 3.B.172.228; 3.B.172.229; 3.B.172.230; 3.B.172.231; 3.B.172.236; 3.B.172.237; 3.B.172.238; 3.B.172.239; 3.B.172.154; 3.B.172.157; 3.B.172.166; 3.B.172.169; 3.B.172.172; 3.B.172.175; 3.B.172.240; 3.B.172.244; 3.B.175.228; 3.B.175.229; 3.B.175.230; 3.B.175.231; 3.B.175.236; 3.B.175.237; 3.B.175.238; 3.B.175.239; 3.B.175.154; 3.B.175.157; 3.B.175.166; 3.B.175.169; 3.B.175.172; 3.B.175.175; 3.B.175.240; 3.B.175.244; 3.B.240.228; 3.B.240.229; 3.B.240.230; 3.B.240.231; 3.B.240.236; 3.B.240.237; 3.B.240.238; 3.B.240.239; 3.B.240.154; 3.B.240.157; 3.B.240.166; 3.B.240.169; 3.B.240.172; 3.B.240.175; 3.B.240.240; 3.B.240.244; 3.B.244.228; 3.B.244.229; 3.B.244.230; 3.B.244.231; 3.B.244.236; 3.B.244.237; 3.B.244.238; 3.B.244.239; 3.B.244.154; 3.B.244.157; 3.B.244.166; 3.B.244.169; 3.B.244.172; 3.B.244.175; 3.B.244.240; 3.B.244.244;

Prodrugs of 3.D

3.D.228.228; 3.D.228.229; 3.D.228.230; 3.D.228.231; 3.D.228.236; 3.D.228.237; 3.D.228.238; 3.D.228.239; 3.D.228.154; 3.D.228.157; 3.D.228.166; 3.D.228.169; 3.D.228.172; 3.D.228.175; 3.D.228.240; 3.D.228.244; 3.D.229.228; 3.D.229.229; 3.D.229.230; 3.D.229.231; 3.D.229.236; 3.D.229.237; 3.D.229.238; 3.D.229.239; 3.D.229.154; 3.D.229.157; 3.D.229.166; 3.D.229.169; 3.D.229.172; 3.D.229.175; 3.D.229.240; 3.D.229.244; 3.D.230.228; 3.D.230.229; 3.D.230.230; 3.D.230.231; 3.D.230.236; 3.D.230.237; 3.D.230.238; 3.D.230.239; 3.D.230.154; 3.D.230.157; 3.D.230.166; 3.D.230.169; 3.D.230.172; 3.D.230.175; 3.D.230.240; 3.D.230.244; 3.D.231.228; 3.D.231.229; 3.D.231.230; 3.D.231.231; 3.D.231.236; 3.D.231.237; 3.D.231.238;

3.D.231.239; 3.D.231.154; 3.D.231.157; 3.D.231.166; 3.D.231.169; 3.D.231.172; 3.D.231.175; 3.D.231.240; 3.D.231.244; 3.D.236.228; 3.D.236.229; 3.D.236.230; 3.D.236.231; 3.D.236.236; 3.D.236.237; 3.D.236.238; 3.D.236.239; 3.D.236.154; 3.D.236.157; 3.D.236.166; 3.D.236.169; 3.D.236.172; 3.D.236.175; 3.D.236.240; 3.D.236.244; 3.D.237.228; 3.D.237.229; 3.D.237.230; 3.D.237.231; 3.D.237.236; 3.D.237.237; 3.D.237.238; 3.D.237.239; 3.D.237.154; 3.D.237.157; 3.D.237.166; 3.D.237.169; 3.D.237.172; 3.D.237.175; 3.D.237.240; 3.D.237.244; 3.D.238.228; 3.D.238.229; 3.D.238.230; 3.D.238.231; 3.D.238.236; 3.D.238.237; 3.D.238.238; 3.D.238.239; 3.D.238.154; 3.D.238.157; 3.D.238.166; 3.D.238.169; 3.D.238.172; 3.D.238.175; 3.D.238.240; 3.D.238.244; 3.D.239.228; 3.D.239.229; 3.D.239.230; 3.D.239.231; 3.D.239.236; 3.D.239.237; 3.D.239.238; 3.D.239.239; 3.D.239.154; 3.D.239.157; 3.D.239.166; 3.D.239.169; 3.D.239.172; 3.D.239.175; 3.D.239.240; 3.D.239.244; 3.D.154.228; 3.D.154.229; 3.D.154.230; 3.D.154.231; 3.D.154.236; 3.D.154.237; 3.D.154.238; 3.D.154.239; 3.D.154.154; 3.D.154.157; 3.D.154.166; 3.D.154.169; 3.D.154.172; 3.D.154.175; 3.D.154.240; 3.D.154.244; 3.D.157.228; 3.D.157.229; 3.D.157.230; 3.D.157.231; 3.D.157.236; 3.D.157.237; 3.D.157.238; 3.D.157.239; 3.D.157.154; 3.D.157.157; 3.D.157.166; 3.D.157.169; 3.D.157.172; 3.D.157.175; 3.D.157.240; 3.D.157.244; 3.D.166.228; 3.D.166.229; 3.D.166.230; 3.D.166.231; 3.D.166.236; 3.D.166.237; 3.D.166.238; 3.D.166.239; 3.D.166.154; 3.D.166.157; 3.D.166.166; 3.D.166.169; 3.D.166.172; 3.D.166.175; 3.D.166.240; 3.D.166.244; 3.D.169.228; 3.D.169.229; 3.D.169.230; 3.D.169.231; 3.D.169.236; 3.D.169.237; 3.D.169.238; 3.D.169.239; 3.D.169.154; 3.D.169.157; 3.D.169.166; 3.D.169.169; 3.D.169.172; 3.D.169.175; 3.D.169.240; 3.D.169.244; 3.D.172.228; 3.D.172.229; 3.D.172.230; 3.D.172.231; 3.D.172.236; 3.D.172.237; 3.D.172.238; 3.D.172.239; 3.D.172.154; 3.D.172.157; 3.D.172.166; 3.D.172.169; 3.D.172.172;

3.D.172.175; 3.D.172.240; 3.D.172.244; 3.D.175.228; 3.D.175.229; 3.D.175.230; 3.D.175.231; 3.D.175.236; 3.D.175.237; 3.D.175.238; 3.D.175.239; 3.D.175.154; 3.D.175.157; 3.D.175.166; 3.D.175.169; 3.D.175.172; 3.D.175.175; 3.D.175.240; 3.D.175.244; 3.D.240.228; 3.D.240.229; 3.D.240.230; 3.D.240.231; 3.D.240.236; 3.D.240.237; 3.D.240.238; 3.D.240.239; 3.D.240.154; 3.D.240.157; 3.D.240.166; 3.D.240.169; 3.D.240.172; 3.D.240.175; 3.D.240.240; 3.D.240.244; 3.D.244.228; 3.D.244.229; 3.D.244.230; 3.D.244.231; 3.D.244.236; 3.D.244.237; 3.D.244.238; 3.D.244.239; 3.D.244.154; 3.D.244.157; 3.D.244.166; 3.D.244.169; 3.D.244.172; 3.D.244.175; 3.D.244.240; 3.D.244.244;

Prodrugs of 3.E

3.E.228.228; 3.E.228.229; 3.E.228.230; 3.E.228.231; 3.E.228.236; 3.E.228.237; 3.E.228.238; 3.E.228.239; 3.E.228.154; 3.E.228.157; 3.E.228.166; 3.E.228.169; 3.E.228.172; 3.E.228.175; 3.E.228.240; 3.E.228.244; 3.E.229.228; 3.E.229.229; 3.E.229.230; 3.E.229.231; 3.E.229.236; 3.E.229.237; 3.E.229.238; 3.E.229.239; 3.E.229.154; 3.E.229.157; 3.E.229.166; 3.E.229.169; 3.E.229.172; 3.E.229.175; 3.E.229.240; 3.E.229.244; 3.E.230.228; 3.E.230.229; 3.E.230.230; 3.E.230.231; 3.E.230.236; 3.E.230.237; 3.E.230.238; 3.E.230.239; 3.E.230.154; 3.E.230.157; 3.E.230.166; 3.E.230.169; 3.E.230.172; 3.E.230.175; 3.E.230.240; 3.E.230.244; 3.E.231.228; 3.E.231.229; 3.E.231.230; 3.E.231.231; 3.E.231.236; 3.E.231.237; 3.E.231.238; 3.E.231.239; 3.E.231.154; 3.E.231.157; 3.E.231.166; 3.E.231.169; 3.E.231.172; 3.E.231.175; 3.E.231.240; 3.E.231.244; 3.E.236.228; 3.E.236.229; 3.E.236.230; 3.E.236.231; 3.E.236.236; 3.E.236.237; 3.E.236.238; 3.E.236.239; 3.E.236.154; 3.E.236.157; 3.E.236.166; 3.E.236.169; 3.E.236.172; 3.E.236.175; 3.E.236.240; 3.E.236.244; 3.E.237.228; 3.E.237.229; 3.E.237.230; 3.E.237.231; 3.E.237.236; 3.E.237.237; 3.E.237.238; 3.E.237.239; 3.E.237.154; 3.E.237.157; 3.E.237.166; 3.E.237.169; 3.E.237.172; 3.E.237.175; 3.E.237.240; 3.E.237.244; 3.E.238.228; 3.E.238.229; 3.E.238.230; 3.E.238.231; 3.E.238.236;

3.E.238.237; 3.E.238.238; 3.E.238.239; 3.E.238.154; 3.E.238.157; 3.E.238.166; 3.E.238.169; 3.E.238.172; 3.E.238.175; 3.E.238.240; 3.E.238.244; 3.E.239.228; 3.E.239.229; 3.E.239.230; 3.E.239.231; 3.E.239.236; 3.E.239.237; 3.E.239.238; 3.E.239.239; 3.E.239.154; 3.E.239.157; 3.E.239.166; 3.E.239.169; 3.E.239.172; 3.E.239.175; 3.E.239.240; 3.E.239.244; 3.E.154.228; 3.E.154.229; 3.E.154.230; 3.E.154.231; 3.E.154.236; 3.E.154.237; 3.E.154.238; 3.E.154.239; 3.E.154.154; 3.E.154.157; 3.E.154.166; 3.E.154.169; 3.E.154.172; 3.E.154.175; 3.E.154.240; 3.E.154.244; 3.E.157.228; 3.E.157.229; 3.E.157.230; 3.E.157.231; 3.E.157.236; 3.E.157.237; 3.E.157.238; 3.E.157.239; 3.E.157.154; 3.E.157.157; 3.E.157.166; 3.E.157.169; 3.E.157.172; 3.E.157.175; 3.E.157.240; 3.E.157.244; 3.E.166.228; 3.E.166.229; 3.E.166.230; 3.E.166.231; 3.E.166.236; 3.E.166.237; 3.E.166.238; 3.E.166.239; 3.E.166.154; 3.E.166.157; 3.E.166.166; 3.E.166.169; 3.E.166.172; 3.E.166.175; 3.E.166.240; 3.E.166.244; 3.E.169.228; 3.E.169.229; 3.E.169.230; 3.E.169.231; 3.E.169.236; 3.E.169.237; 3.E.169.238; 3.E.169.239; 3.E.169.154; 3.E.169.157; 3.E.169.166; 3.E.169.169; 3.E.169.172; 3.E.169.175; 3.E.169.240; 3.E.169.244; 3.E.172.228; 3.E.172.229; 3.E.172.230; 3.E.172.231; 3.E.172.236; 3.E.172.237; 3.E.172.238; 3.E.172.239; 3.E.172.154; 3.E.172.157; 3.E.172.166; 3.E.172.169; 3.E.172.172; 3.E.172.175; 3.E.172.240; 3.E.172.244; 3.E.175.228; 3.E.175.229; 3.E.175.230; 3.E.175.231; 3.E.175.236; 3.E.175.237; 3.E.175.238; 3.E.175.239; 3.E.175.154; 3.E.175.157; 3.E.175.166; 3.E.175.169; 3.E.175.172; 3.E.175.175; 3.E.175.240; 3.E.175.244; 3.E.240.228; 3.E.240.229; 3.E.240.230; 3.E.240.231; 3.E.240.236; 3.E.240.237; 3.E.240.238; 3.E.240.239; 3.E.240.154; 3.E.240.157; 3.E.240.166; 3.E.240.169; 3.E.240.172; 3.E.240.175; 3.E.240.240; 3.E.240.244; 3.E.244.228; 3.E.244.229; 3.E.244.230; 3.E.244.231; 3.E.244.236; 3.E.244.237; 3.E.244.238; 3.E.244.239; 3.E.244.154; 3.E.244.157; 3.E.244.166; 3.E.244.169; 3.E.244.172; 3.E.244.175; 3.E.244.240; 3.E.244.244;

Prodrugs of 3.G

3.G.228.228; 3.G.228.229; 3.G.228.230; 3.G.228.231; 3.G.228.236; 3.G.228.237; 3.G.228.238; 3.G.228.239; 3.G.228.154; 3.G.228.157;

3.G.228.166; 3.G.228.169; 3.G.228.172; 3.G.228.175; 3.G.228.240; 3.G.228.244; 3.G.229.228; 3.G.229.229; 3.G.229.230; 3.G.229.231; 3.G.229.236; 3.G.229.237; 3.G.229.238; 3.G.229.239; 3.G.229.154; 3.G.229.157; 3.G.229.166; 3.G.229.169; 3.G.229.172; 3.G.229.175; 3.G.229.240; 3.G.229.244; 3.G.230.228; 3.G.230.229; 3.G.230.230; 3.G.230.231; 3.G.230.236; 3.G.230.237; 3.G.230.238; 3.G.230.239; 3.G.230.154; 3.G.230.157; 3.G.230.166; 3.G.230.169; 3.G.230.172; 3.G.230.175; 3.G.230.240; 3.G.230.244; 3.G.231.228; 3.G.231.229; 3.G.231.230; 3.G.231.231; 3.G.231.236; 3.G.231.237; 3.G.231.238; 3.G.231.239; 3.G.231.154; 3.G.231.157; 3.G.231.166; 3.G.231.169; 3.G.231.172; 3.G.231.175; 3.G.231.240; 3.G.231.244; 3.G.236.228; 3.G.236.229; 3.G.236.230; 3.G.236.231; 3.G.236.236; 3.G.236.237; 3.G.236.238; 3.G.236.239; 3.G.236.154; 3.G.236.157; 3.G.236.166; 3.G.236.169; 3.G.236.172; 3.G.236.175; 3.G.236.240; 3.G.236.244; 3.G.237.228; 3.G.237.229; 3.G.237.230; 3.G.237.231; 3.G.237.236; 3.G.237.237; 3.G.237.238; 3.G.237.239; 3.G.237.154; 3.G.237.157; 3.G.237.166; 3.G.237.169; 3.G.237.172; 3.G.237.175; 3.G.237.240; 3.G.237.244; 3.G.238.228; 3.G.238.229; 3.G.238.230; 3.G.238.231; 3.G.238.236; 3.G.238.237; 3.G.238.238; 3.G.238.239; 3.G.238.154; 3.G.238.157; 3.G.238.166; 3.G.238.169; 3.G.238.172; 3.G.238.175; 3.G.238.240; 3.G.238.244; 3.G.239.228; 3.G.239.229; 3.G.239.230; 3.G.239.231; 3.G.239.236; 3.G.239.237; 3.G.239.238; 3.G.239.239; 3.G.239.154; 3.G.239.157; 3.G.239.166; 3.G.239.169; 3.G.239.172; 3.G.239.175; 3.G.239.240; 3.G.239.244; 3.G.154.228; 3.G.154.229; 3.G.154.230; 3.G.154.231; 3.G.154.236; 3.G.154.237; 3.G.154.238; 3.G.154.239; 3.G.154.154; 3.G.154.157; 3.G.154.166; 3.G.154.169; 3.G.154.172; 3.G.154.175; 3.G.154.240; 3.G.154.244; 3.G.157.228; 3.G.157.229; 3.G.157.230; 3.G.157.231; 3.G.157.236; 3.G.157.237; 3.G.157.238; 3.G.157.239; 3.G.157.154; 3.G.157.157; 3.G.157.166; 3.G.157.169; 3.G.157.172; 3.G.157.175; 3.G.157.240; 3.G.157.244;

3.G.166.228; 3.G.166.229; 3.G.166.230; 3.G.166.231; 3.G.166.236; 3.G.166.237; 3.G.166.238; 3.G.166.239; 3.G.166.154; 3.G.166.157; 3.G.166.166; 3.G.166.169; 3.G.166.172; 3.G.166.175; 3.G.166.240; 3.G.166.244; 3.G.169.228; 3.G.169.229; 3.G.169.230; 3.G.169.231; 3.G.169.236; 3.G.169.237; 3.G.169.238; 3.G.169.239; 3.G.169.154; 3.G.169.157; 3.G.169.166; 3.G.169.169; 3.G.169.172; 3.G.169.175; 3.G.169.240; 3.G.169.244; 3.G.172.228; 3.G.172.229; 3.G.172.230; 3.G.172.231; 3.G.172.236; 3.G.172.237; 3.G.172.238; 3.G.172.239; 3.G.172.154; 3.G.172.157; 3.G.172.166; 3.G.172.169; 3.G.172.172; 3.G.172.175; 3.G.172.240; 3.G.172.244; 3.G.175.228; 3.G.175.229; 3.G.175.230; 3.G.175.231; 3.G.175.236; 3.G.175.237; 3.G.175.238; 3.G.175.239; 3.G.175.154; 3.G.175.157; 3.G.175.166; 3.G.175.169; 3.G.175.172; 3.G.175.175; 3.G.175.240; 3.G.175.244; 3.G.240.228; 3.G.240.229; 3.G.240.230; 3.G.240.231; 3.G.240.236; 3.G.240.237; 3.G.240.238; 3.G.240.239; 3.G.240.154; 3.G.240.157; 3.G.240.166; 3.G.240.169; 3.G.240.172; 3.G.240.175; 3.G.240.240; 3.G.240.244; 3.G.244.228; 3.G.244.229; 3.G.244.230; 3.G.244.231; 3.G.244.236; 3.G.244.237; 3.G.244.238; 3.G.244.239; 3.G.244.154; 3.G.244.157; 3.G.244.166; 3.G.244.169; 3.G.244.172; 3.G.244.175; 3.G.244.240; 3.G.244.244;

Prodrugs of 3.I

3.I.228.228; 3.I.228.229; 3.I.228.230; 3.I.228.231; 3.I.228.236; 3.I.228.237; 3.I.228.238; 3.I.228.239; 3.I.228.154; 3.I.228.157; 3.I.228.166; 3.I.228.169; 3.I.228.172; 3.I.228.175; 3.I.228.240; 3.I.228.244; 3.I.229.228; 3.I.229.229; 3.I.229.230; 3.I.229.231; 3.I.229.236; 3.I.229.237; 3.I.229.238; 3.I.229.239; 3.I.229.154; 3.I.229.157; 3.I.229.166; 3.I.229.169; 3.I.229.172; 3.I.229.175; 3.I.229.240; 3.I.229.244; 3.I.230.228; 3.I.230.229; 3.I.230.230; 3.I.230.231; 3.I.230.236; 3.I.230.237; 3.I.230.238; 3.I.230.239; 3.I.230.154; 3.I.230.157; 3.I.230.166; 3.I.230.169; 3.I.230.172; 3.I.230.175; 3.I.230.240; 3.I.230.244;

3.I.231.228; 3.I.231.229; 3.I.231.230; 3.I.231.231; 3.I.231.236; 3.I.231.237; 3.I.231.238; 3.I.231.239; 3.I.231.154; 3.I.231.157; 3.I.231.166; 3.I.231.169; 3.I.231.172; 3.I.231.175; 3.I.231.240; 3.I.231.244; 3.I.236.228; 3.I.236.229; 3.I.236.230; 3.I.236.231; 3.I.236.236; 3.I.236.237; 3.I.236.238; 3.I.236.239; 3.I.236.154; 3.I.236.157; 3.I.236.166; 3.I.236.169; 3.I.236.172; 3.I.236.175; 3.I.236.240; 3.I.236.244; 3.I.237.228; 3.I.237.229; 3.I.237.230; 3.I.237.231; 3.I.237.236; 3.I.237.237; 3.I.237.238; 3.I.237.239; 3.I.237.154; 3.I.237.157; 3.I.237.166; 3.I.237.169; 3.I.237.172; 3.I.237.175; 3.I.237.240; 3.I.237.244; 3.I.238.228; 3.I.238.229; 3.I.238.230; 3.I.238.231; 3.I.238.236; 3.I.238.237; 3.I.238.238; 3.I.238.239; 3.I.238.154; 3.I.238.157; 3.I.238.166; 3.I.238.169; 3.I.238.172; 3.I.238.175; 3.I.238.240; 3.I.238.244; 3.I.239.228; 3.I.239.229; 3.I.239.230; 3.I.239.231; 3.I.239.236; 3.I.239.237; 3.I.239.238; 3.I.239.239; 3.I.239.154; 3.I.239.157; 3.I.239.166; 3.I.239.169; 3.I.239.172; 3.I.239.175; 3.I.239.240; 3.I.239.244; 3.I.154.228; 3.I.154.229; 3.I.154.230; 3.I.154.231; 3.I.154.236; 3.I.154.237; 3.I.154.238; 3.I.154.239; 3.I.154.154; 3.I.154.157; 3.I.154.166; 3.I.154.169; 3.I.154.172; 3.I.154.175; 3.I.154.240; 3.I.154.244; 3.I.157.228; 3.I.157.229; 3.I.157.230; 3.I.157.231; 3.I.157.236; 3.I.157.237; 3.I.157.238; 3.I.157.239; 3.I.157.154; 3.I.157.157; 3.I.157.166; 3.I.157.169; 3.I.157.172; 3.I.157.175; 3.I.157.240; 3.I.157.244; 3.I.166.228; 3.I.166.229; 3.I.166.230; 3.I.166.231; 3.I.166.236; 3.I.166.237; 3.I.166.238; 3.I.166.239; 3.I.166.154; 3.I.166.157; 3.I.166.166; 3.I.166.169; 3.I.166.172; 3.I.166.175; 3.I.166.240; 3.I.166.244; 3.I.169.228; 3.I.169.229; 3.I.169.230; 3.I.169.231; 3.I.169.236; 3.I.169.237; 3.I.169.238; 3.I.169.239; 3.I.169.154; 3.I.169.157; 3.I.169.166; 3.I.169.169; 3.I.169.172; 3.I.169.175; 3.I.169.240; 3.I.169.244; 3.I.172.228; 3.I.172.229; 3.I.172.230; 3.I.172.231; 3.I.172.236; 3.I.172.237; 3.I.172.238; 3.I.172.239; 3.I.172.154; 3.I.172.157; 3.I.172.166; 3.I.172.169; 3.I.172.172; 3.I.172.175; 3.I.172.240; 3.I.172.244; 3.I.175.228; 3.I.175.229; 3.I.175.230; 3.I.175.231; 3.I.175.236; 3.I.175.237; 3.I.175.238; 3.I.175.239; 3.I.175.154; 3.I.175.157; 3.I.175.166; 3.I.175.169; 3.I.175.172; 3.I.175.175; 3.I.175.240; 3.I.175.244; 3.I.240.228; 3.I.240.229; 3.I.240.230; 3.I.240.231;

3.I.240.236; 3.I.240.237; 3.I.240.238; 3.I.240.239; 3.I.240.154; 3.I.240.157; 3.I.240.166; 3.I.240.169; 3.I.240.172; 3.I.240.175; 3.I.240.240; 3.I.240.244; 3.I.244.228; 3.I.244.229; 3.I.244.230; 3.I.244.231; 3.I.244.236; 3.I.244.237; 3.I.244.238; 3.I.244.239; 3.I.244.154; 3.I.244.157; 3.I.244.166; 3.I.244.169; 3.I.244.172; 3.I.244.175; 3.I.244.240; 3.I.244.244;

Prodrugs of 3.J

3.J.228.228; 3.J.228.229; 3.J.228.230; 3.J.228.231; 3.J.228.236; 3.J.228.237; 3.J.228.238; 3.J.228.239; 3.J.228.154; 3.J.228.157; 3.J.228.166; 3.J.228.169; 3.J.228.172; 3.J.228.175; 3.J.228.240; 3.J.228.244; 3.J.229.228; 3.J.229.229; 3.J.229.230; 3.J.229.231; 3.J.229.236; 3.J.229.237; 3.J.229.238; 3.J.229.239; 3.J.229.154; 3.J.229.157; 3.J.229.166; 3.J.229.169; 3.J.229.172; 3.J.229.175; 3.J.229.240; 3.J.229.244; 3.J.230.228; 3.J.230.229; 3.J.230.230; 3.J.230.231; 3.J.230.236; 3.J.230.237; 3.J.230.238; 3.J.230.239; 3.J.230.154; 3.J.230.157; 3.J.230.166; 3.J.230.169; 3.J.230.172; 3.J.230.175; 3.J.230.240; 3.J.230.244; 3.J.231.228; 3.J.231.229; 3.J.231.230; 3.J.231.231; 3.J.231.236; 3.J.231.237; 3.J.231.238; 3.J.231.239; 3.J.231.154; 3.J.231.157; 3.J.231.166; 3.J.231.169; 3.J.231.172; 3.J.231.175; 3.J.231.240; 3.J.231.244; 3.J.236.228; 3.J.236.229; 3.J.236.230; 3.J.236.231; 3.J.236.236; 3.J.236.237; 3.J.236.238; 3.J.236.239; 3.J.236.154; 3.J.236.157; 3.J.236.166; 3.J.236.169; 3.J.236.172; 3.J.236.175; 3.J.236.240; 3.J.236.244; 3.J.237.228; 3.J.237.229; 3.J.237.230; 3.J.237.231; 3.J.237.236; 3.J.237.237; 3.J.237.238; 3.J.237.239; 3.J.237.154; 3.J.237.157; 3.J.237.166; 3.J.237.169; 3.J.237.172; 3.J.237.175; 3.J.237.240; 3.J.237.244; 3.J.238.228; 3.J.238.229; 3.J.238.230; 3.J.238.231; 3.J.238.236; 3.J.238.237; 3.J.238.238; 3.J.238.239; 3.J.238.154; 3.J.238.157; 3.J.238.166; 3.J.238.169; 3.J.238.172; 3.J.238.175; 3.J.238.240; 3.J.238.244; 3.J.239.228; 3.J.239.229; 3.J.239.230; 3.J.239.231; 3.J.239.236; 3.J.239.237; 3.J.239.238; 3.J.239.239; 3.J.239.154; 3.J.239.157; 3.J.239.166; 3.J.239.169; 3.J.239.172; 3.J.239.175; 3.J.239.240; 3.J.239.244; 3.J.154.228; 3.J.154.229; 3.J.154.230; 3.J.154.231; 3.J.154.236; 3.J.154.237; 3.J.154.238; 3.J.154.239; 3.J.154.154; 3.J.154.157;

3.J.154.166; 3.J.154.169; 3.J.154.172; 3.J.154.175; 3.J.154.240; 3.J.154.244; 3.J.157.228; 3.J.157.229; 3.J.157.230; 3.J.157.231; 3.J.157.236; 3.J.157.237; 3.J.157.238; 3.J.157.239; 3.J.157.154; 3.J.157.157; 3.J.157.166; 3.J.157.169; 3.J.157.172; 3.J.157.175; 3.J.157.240; 3.J.157.244; 3.J.166.228; 3.J.166.229; 3.J.166.230; 3.J.166.231; 3.J.166.236; 3.J.166.237; 3.J.166.238; 3.J.166.239; 3.J.166.154; 3.J.166.157; 3.J.166.166; 3.J.166.169; 3.J.166.172; 3.J.166.175; 3.J.166.240; 3.J.166.244; 3.J.169.228; 3.J.169.229; 3.J.169.230; 3.J.169.231; 3.J.169.236; 3.J.169.237; 3.J.169.238; 3.J.169.239; 3.J.169.154; 3.J.169.157; 3.J.169.166; 3.J.169.169; 3.J.169.172; 3.J.169.175; 3.J.169.240; 3.J.169.244; 3.J.172.228; 3.J.172.229; 3.J.172.230; 3.J.172.231; 3.J.172.236; 3.J.172.237; 3.J.172.238; 3.J.172.239; 3.J.172.154; 3.J.172.157; 3.J.172.166; 3.J.172.169; 3.J.172.172; 3.J.172.175; 3.J.172.240; 3.J.172.244; 3.J.175.228; 3.J.175.229; 3.J.175.230; 3.J.175.231; 3.J.175.236; 3.J.175.237; 3.J.175.238; 3.J.175.239; 3.J.175.154; 3.J.175.157; 3.J.175.166; 3.J.175.169; 3.J.175.172; 3.J.175.175; 3.J.175.240; 3.J.175.244; 3.J.240.228; 3.J.240.229; 3.J.240.230; 3.J.240.231; 3.J.240.236; 3.J.240.237; 3.J.240.238; 3.J.240.239; 3.J.240.154; 3.J.240.157; 3.J.240.166; 3.J.240.169; 3.J.240.172; 3.J.240.175; 3.J.240.240; 3.J.240.244; 3.J.244.228; 3.J.244.229; 3.J.244.230; 3.J.244.231; 3.J.244.236; 3.J.244.237; 3.J.244.238; 3.J.244.239; 3.J.244.154; 3.J.244.157; 3.J.244.166; 3.J.244.169; 3.J.244.172; 3.J.244.175; 3.J.244.240; 3.J.244.244;

Prodrugs of 3.L

3.L.228.228; 3.L.228.229; 3.L.228.230; 3.L.228.231; 3.L.228.236; 3.L.228.237; 3.L.228.238; 3.L.228.239; 3.L.228.154; 3.L.228.157; 3.L.228.166; 3.L.228.169; 3.L.228.172; 3.L.228.175; 3.L.228.240; 3.L.228.244; 3.L.229.228; 3.L.229.229; 3.L.229.230; 3.L.229.231; 3.L.229.236; 3.L.229.237; 3.L.229.238; 3.L.229.239; 3.L.229.154; 3.L.229.157; 3.L.229.166; 3.L.229.169; 3.L.229.172; 3.L.229.175; 3.L.229.240; 3.L.229.244; 3.L.230.228; 3.L.230.229; 3.L.230.230; 3.L.230.231; 3.L.230.236; 3.L.230.237; 3.L.230.238; 3.L.230.239; 3.L.230.154; 3.L.230.157; 3.L.230.166; 3.L.230.169; 3.L.230.172; 3.L.230.175; 3.L.230.240;

3.L.230.244; 3.L.231.228; 3.L.231.229; 3.L.231.230; 3.L.231.231; 3.L.231.236; 3.L.231.237; 3.L.231.238; 3.L.231.239; 3.L.231.154; 3.L.231.157; 3.L.231.166; 3.L.231.169; 3.L.231.172; 3.L.231.175; 3.L.231.240; 3.L.231.244; 3.L.236.228; 3.L.236.229; 3.L.236.230; 3.L.236.231; 3.L.236.236; 3.L.236.237; 3.L.236.238; 3.L.236.239; 3.L.236.154; 3.L.236.157; 3.L.236.166; 3.L.236.169; 3.L.236.172; 3.L.236.175; 3.L.236.240; 3.L.236.244; 3.L.237.228; 3.L.237.229; 3.L.237.230; 3.L.237.231; 3.L.237.236; 3.L.237.237; 3.L.237.238; 3.L.237.239; 3.L.237.154; 3.L.237.157; 3.L.237.166; 3.L.237.169; 3.L.237.172; 3.L.237.175; 3.L.237.240; 3.L.237.244; 3.L.238.228; 3.L.238.229; 3.L.238.230; 3.L.238.231; 3.L.238.236; 3.L.238.237; 3.L.238.238; 3.L.238.239; 3.L.238.154; 3.L.238.157; 3.L.238.166; 3.L.238.169; 3.L.238.172; 3.L.238.175; 3.L.238.240; 3.L.238.244; 3.L.239.228; 3.L.239.229; 3.L.239.230; 3.L.239.231; 3.L.239.236; 3.L.239.237; 3.L.239.238; 3.L.239.239; 3.L.239.154; 3.L.239.157; 3.L.239.166; 3.L.239.169; 3.L.239.172; 3.L.239.175; 3.L.239.240; 3.L.239.244; 3.L.154.228; 3.L.154.229; 3.L.154.230; 3.L.154.231; 3.L.154.236; 3.L.154.237; 3.L.154.238; 3.L.154.239; 3.L.154.154; 3.L.154.157; 3.L.154.166; 3.L.154.169; 3.L.154.172; 3.L.154.175; 3.L.154.240; 3.L.154.244; 3.L.157.228; 3.L.157.229; 3.L.157.230; 3.L.157.231; 3.L.157.236; 3.L.157.237; 3.L.157.238; 3.L.157.239; 3.L.157.154; 3.L.157.157; 3.L.157.166; 3.L.157.169; 3.L.157.172; 3.L.157.175; 3.L.157.240; 3.L.157.244; 3.L.166.228; 3.L.166.229; 3.L.166.230; 3.L.166.231; 3.L.166.236; 3.L.166.237; 3.L.166.238; 3.L.166.239; 3.L.166.154; 3.L.166.157; 3.L.166.166; 3.L.166.169; 3.L.166.172; 3.L.166.175; 3.L.166.240; 3.L.166.244; 3.L.169.228; 3.L.169.229; 3.L.169.230; 3.L.169.231; 3.L.169.236; 3.L.169.237; 3.L.169.238; 3.L.169.239; 3.L.169.154; 3.L.169.157; 3.L.169.166; 3.L.169.169; 3.L.169.172; 3.L.169.175; 3.L.169.240; 3.L.169.244; 3.L.172.228; 3.L.172.229; 3.L.172.230; 3.L.172.231; 3.L.172.236; 3.L.172.237; 3.L.172.238; 3.L.172.239; 3.L.172.154; 3.L.172.157; 3.L.172.166; 3.L.172.169; 3.L.172.172; 3.L.172.175; 3.L.172.240; 3.L.172.244; 3.L.175.228; 3.L.175.229; 3.L.175.230; 3.L.175.231; 3.L.175.236; 3.L.175.237; 3.L.175.238; 3.L.175.239; 3.L.175.154; 3.L.175.157; 3.L.175.166; 3.L.175.169; 3.L.175.172; 3.L.175.175; 3.L.175.240; 3.L.175.244; 3.L.240.228; 3.L.240.229; 3.L.240.230;

3.L.240.231; 3.L.240.236; 3.L.240.237; 3.L.240.238; 3.L.240.239; 3.L.240.154; 3.L.240.157; 3.L.240.166; 3.L.240.169; 3.L.240.172; 3.L.240.175; 3.L.240.240; 3.L.240.244; 3.L.244.228; 3.L.244.229; 3.L.244.230; 3.L.244.231; 3.L.244.236; 3.L.244.237; 3.L.244.238; 3.L.244.239; 3.L.244.154; 3.L.244.157; 3.L.244.166; 3.L.244.169; 3.L.244.172; 3.L.244.175; 3.L.244.240; 3.L.244.244;

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3.O.228.228; 3.O.228.229; 3.O.228.230; 3.O.228.231; 3.O.228.236; 3.O.228.237; 3.O.228.238; 3.O.228.239; 3.O.228.154; 3.O.228.157; 3.O.228.166; 3.O.228.169; 3.O.228.172; 3.O.228.175; 3.O.228.240; 3.O.228.244; 3.O.229.228; 3.O.229.229; 3.O.229.230; 3.O.229.231; 3.O.229.236; 3.O.229.237; 3.O.229.238; 3.O.229.239; 3.O.229.154; 3.O.229.157; 3.O.229.166; 3.O.229.169; 3.O.229.172; 3.O.229.175; 3.O.229.240; 3.O.229.244; 3.O.230.228; 3.O.230.229; 3.O.230.230; 3.O.230.231; 3.O.230.236; 3.O.230.237; 3.O.230.238; 3.O.230.239; 3.O.230.154; 3.O.230.157; 3.O.230.166; 3.O.230.169; 3.O.230.172; 3.O.230.175; 3.O.230.240; 3.O.230.244; 3.O.231.228; 3.O.231.229; 3.O.231.230; 3.O.231.231; 3.O.231.236; 3.O.231.237; 3.O.231.238; 3.O.231.239; 3.O.231.154; 3.O.231.157; 3.O.231.166; 3.O.231.169; 3.O.231.172; 3.O.231.175; 3.O.231.240; 3.O.231.244; 3.O.236.228; 3.O.236.229; 3.O.236.230; 3.O.236.231; 3.O.236.236; 3.O.236.237; 3.O.236.238; 3.O.236.239; 3.O.236.154; 3.O.236.157; 3.O.236.166; 3.O.236.169; 3.O.236.172; 3.O.236.175; 3.O.236.240; 3.O.236.244; 3.O.237.228; 3.O.237.229; 3.O.237.230; 3.O.237.231; 3.O.237.236; 3.O.237.237; 3.O.237.238; 3.O.237.239; 3.O.237.154; 3.O.237.157; 3.O.237.166; 3.O.237.169; 3.O.237.172; 3.O.237.175; 3.O.237.240; 3.O.237.244; 3.O.238.228; 3.O.238.229; 3.O.238.230; 3.O.238.231; 3.O.238.236; 3.O.238.237; 3.O.238.238; 3.O.238.239; 3.O.238.154; 3.O.238.157; 3.O.238.166; 3.O.238.169; 3.O.238.172; 3.O.238.175; 3.O.238.240; 3.O.238.244; 3.O.239.228; 3.O.239.229; 3.O.239.230;

3.O.239.231; 3.O.239.236; 3.O.239.237; 3.O.239.238; 3.O.239.239; 3.O.239.154; 3.O.239.157; 3.O.239.166; 3.O.239.169; 3.O.239.172; 3.O.239.175; 3.O.239.240; 3.O.239.244; 3.O.154.228; 3.O.154.229; 3.O.154.230; 3.O.154.231; 3.O.154.236; 3.O.154.237; 3.O.154.238; 3.O.154.239; 3.O.154.154; 3.O.154.157; 3.O.154.166; 3.O.154.169; 3.O.154.172; 3.O.154.175; 3.O.154.240; 3.O.154.244; 3.O.157.228; 3.O.157.229; 3.O.157.230; 3.O.157.231; 3.O.157.236; 3.O.157.237; 3.O.157.238; 3.O.157.239; 3.O.157.154; 3.O.157.157; 3.O.157.166; 3.O.157.169; 3.O.157.172; 3.O.157.175; 3.O.157.240; 3.O.157.244; 3.O.166.228; 3.O.166.229; 3.O.166.230; 3.O.166.231; 3.O.166.236; 3.O.166.237; 3.O.166.238; 3.O.166.239; 3.O.166.154; 3.O.166.157; 3.O.166.166; 3.O.166.169; 3.O.166.172; 3.O.166.175; 3.O.166.240; 3.O.166.244; 3.O.169.228; 3.O.169.229; 3.O.169.230; 3.O.169.231; 3.O.169.236; 3.O.169.237; 3.O.169.238; 3.O.169.239; 3.O.169.154; 3.O.169.157; 3.O.169.166; 3.O.169.169; 3.O.169.172; 3.O.169.175; 3.O.169.240; 3.O.169.244; 3.O.172.228; 3.O.172.229; 3.O.172.230; 3.O.172.231; 3.O.172.236; 3.O.172.237; 3.O.172.238; 3.O.172.239; 3.O.172.154; 3.O.172.157; 3.O.172.166; 3.O.172.169; 3.O.172.172; 3.O.172.175; 3.O.172.240; 3.O.172.244; 3.O.175.228; 3.O.175.229; 3.O.175.230; 3.O.175.231; 3.O.175.236; 3.O.175.237; 3.O.175.238; 3.O.175.239; 3.O.175.154; 3.O.175.157; 3.O.175.166; 3.O.175.169; 3.O.175.172; 3.O.175.175; 3.O.175.240; 3.O.175.244; 3.O.240.228; 3.O.240.229; 3.O.240.230; 3.O.240.231; 3.O.240.236; 3.O.240.237; 3.O.240.238; 3.O.240.239; 3.O.240.154; 3.O.240.157; 3.O.240.166; 3.O.240.169; 3.O.240.172; 3.O.240.175; 3.O.240.240; 3.O.240.244; 3.O.244.228; 3.O.244.229; 3.O.244.230; 3.O.244.231; 3.O.244.236; 3.O.244.237; 3.O.244.238; 3.O.244.239; 3.O.244.154; 3.O.244.157; 3.O.244.166; 3.O.244.169; 3.O.244.172; 3.O.244.175; 3.O.244.240; 3.O.244.244;

Prodrugs of 3.P

3.P.228.228; 3.P.228.229; 3.P.228.230; 3.P.228.231; 3.P.228.236; 3.P.228.237; 3.P.228.238; 3.P.228.239; 3.P.228.154; 3.P.228.157; 3.P.228.166; 3.P.228.169; 3.P.228.172; 3.P.228.175; 3.P.228.240; 3.P.228.244; 3.P.229.228; 3.P.229.229; 3.P.229.230; 3.P.229.231; 3.P.229.236; 3.P.229.237; 3.P.229.238; 3.P.229.239; 3.P.229.154; 3.P.229.157; 3.P.229.166; 3.P.229.169; 3.P.229.172; 3.P.229.175; 3.P.229.240; 3.P.229.244; 3.P.230.228; 3.P.230.229; 3.P.230.230; 3.P.230.231; 3.P.230.236; 3.P.230.237; 3.P.230.238; 3.P.230.239; 3.P.230.154; 3.P.230.157; 3.P.230.166; 3.P.230.169; 3.P.230.172; 3.P.230.175; 3.P.230.240; 3.P.230.244; 3.P.231.228; 3.P.231.229; 3.P.231.230; 3.P.231.231; 3.P.231.236; 3.P.231.237; 3.P.231.238; 3.P.231.239; 3.P.231.154; 3.P.231.157; 3.P.231.166; 3.P.231.169; 3.P.231.172; 3.P.231.175; 3.P.231.240; 3.P.231.244; 3.P.236.228; 3.P.236.229; 3.P.236.230; 3.P.236.231; 3.P.236.236; 3.P.236.237; 3.P.236.238; 3.P.236.239; 3.P.236.154; 3.P.236.157; 3.P.236.166; 3.P.236.169; 3.P.236.172; 3.P.236.175; 3.P.236.240; 3.P.236.244; 3.P.237.228; 3.P.237.229; 3.P.237.230; 3.P.237.231; 3.P.237.236; 3.P.237.237; 3.P.237.238; 3.P.237.239; 3.P.237.154; 3.P.237.157; 3.P.237.166; 3.P.237.169; 3.P.237.172; 3.P.237.175; 3.P.237.240; 3.P.237.244; 3.P.238.228; 3.P.238.229; 3.P.238.230; 3.P.238.231; 3.P.238.236; 3.P.238.237; 3.P.238.238; 3.P.238.239; 3.P.238.154; 3.P.238.157; 3.P.238.166; 3.P.238.169; 3.P.238.172; 3.P.238.175; 3.P.238.240; 3.P.238.244; 3.P.239.228; 3.P.239.229; 3.P.239.230; 3.P.239.231; 3.P.239.236; 3.P.239.237; 3.P.239.238; 3.P.239.239; 3.P.239.154; 3.P.239.157; 3.P.239.166; 3.P.239.169; 3.P.239.172; 3.P.239.175; 3.P.239.240; 3.P.239.244; 3.P.154.228; 3.P.154.229; 3.P.154.230; 3.P.154.231; 3.P.154.236; 3.P.154.237; 3.P.154.238; 3.P.154.239; 3.P.154.154; 3.P.154.157; 3.P.154.166; 3.P.154.169; 3.P.154.172; 3.P.154.175; 3.P.154.240; 3.P.154.244; 3.P.157.228; 3.P.157.229; 3.P.157.230; 3.P.157.231; 3.P.157.236; 3.P.157.237; 3.P.157.238; 3.P.157.239; 3.P.157.154; 3.P.157.157; 3.P.157.166; 3.P.157.169; 3.P.157.172; 3.P.157.175; 3.P.157.240; 3.P.157.244; 3.P.166.228; 3.P.166.229; 3.P.166.230; 3.P.166.231; 3.P.166.236; 3.P.166.237; 3.P.166.238; 3.P.166.239; 3.P.166.154; 3.P.166.157; 3.P.166.166; 3.P.166.169; 3.P.166.172;

3.P.166.175; 3.P.166.240; 3.P.166.244; 3.P.169.228; 3.P.169.229; 3.P.169.230; 3.P.169.231; 3.P.169.236; 3.P.169.237; 3.P.169.238; 3.P.169.239; 3.P.169.154; 3.P.169.157; 3.P.169.166; 3.P.169.169; 3.P.169.172; 3.P.169.175; 3.P.169.240; 3.P.169.244; 3.P.172.228; 3.P.172.229; 3.P.172.230; 3.P.172.231; 3.P.172.236; 3.P.172.237; 3.P.172.238; 3.P.172.239; 3.P.172.154; 3.P.172.157; 3.P.172.166; 3.P.172.169; 3.P.172.172; 3.P.172.175; 3.P.172.240; 3.P.172.244; 3.P.175.228; 3.P.175.229; 3.P.175.230; 3.P.175.231; 3.P.175.236; 3.P.175.237; 3.P.175.238; 3.P.175.239; 3.P.175.154; 3.P.175.157; 3.P.175.166; 3.P.175.169; 3.P.175.172; 3.P.175.175; 3.P.175.240; 3.P.175.244; 3.P.240.228; 3.P.240.229; 3.P.240.230; 3.P.240.231; 3.P.240.236; 3.P.240.237; 3.P.240.238; 3.P.240.239; 3.P.240.154; 3.P.240.157; 3.P.240.166; 3.P.240.169; 3.P.240.172; 3.P.240.175; 3.P.240.240; 3.P.240.244; 3.P.244.228; 3.P.244.229; 3.P.244.230; 3.P.244.231; 3.P.244.236; 3.P.244.237; 3.P.244.238; 3.P.244.239; 3.P.244.154; 3.P.244.157; 3.P.244.166; 3.P.244.169; 3.P.244.172; 3.P.244.175; 3.P.244.240; 3.P.244.244;

Prodrugs of 3.U

3.U.228.228; 3.U.228.229; 3.U.228.230; 3.U.228.231; 3.U.228.236; 3.U.228.237; 3.U.228.238; 3.U.228.239; 3.U.228.154; 3.U.228.157; 3.U.228.166; 3.U.228.169; 3.U.228.172; 3.U.228.175; 3.U.228.240; 3.U.228.244; 3.U.229.228; 3.U.229.229; 3.U.229.230; 3.U.229.231; 3.U.229.236; 3.U.229.237; 3.U.229.238; 3.U.229.239; 3.U.229.154; 3.U.229.157; 3.U.229.166; 3.U.229.169; 3.U.229.172; 3.U.229.175; 3.U.229.240; 3.U.229.244; 3.U.230.228; 3.U.230.229; 3.U.230.230; 3.U.230.231; 3.U.230.236; 3.U.230.237; 3.U.230.238; 3.U.230.239; 3.U.230.154; 3.U.230.157; 3.U.230.166; 3.U.230.169; 3.U.230.172; 3.U.230.175; 3.U.230.240; 3.U.230.244; 3.U.231.228; 3.U.231.229; 3.U.231.230; 3.U.231.231; 3.U.231.236; 3.U.231.237; 3.U.231.238; 3.U.231.239; 3.U.231.154; 3.U.231.157; 3.U.231.166; 3.U.231.169; 3.U.231.172; 3.U.231.175; 3.U.231.240; 3.U.231.244; 3.U.236.228; 3.U.236.229; 3.U.236.230; 3.U.236.231; 3.U.236.236; 3.U.236.237;

3.U.236.238; 3.U.236.239; 3.U.236.154; 3.U.236.157; 3.U.236.166; 3.U.236.169; 3.U.236.172; 3.U.236.175; 3.U.236.240; 3.U.236.244; 3.U.237.228; 3.U.237.229; 3.U.237.230; 3.U.237.231; 3.U.237.236; 3.U.237.237; 3.U.237.238; 3.U.237.239; 3.U.237.154; 3.U.237.157; 3.U.237.166; 3.U.237.169; 3.U.237.172; 3.U.237.175; 3.U.237.240; 3.U.237.244; 3.U.238.228; 3.U.238.229; 3.U.238.230; 3.U.238.231; 3.U.238.236; 3.U.238.237; 3.U.238.238; 3.U.238.239; 3.U.238.154; 3.U.238.157; 3.U.238.166; 3.U.238.169; 3.U.238.172; 3.U.238.175; 3.U.238.240; 3.U.238.244; 3.U.239.228; 3.U.239.229; 3.U.239.230; 3.U.239.231; 3.U.239.236; 3.U.239.237; 3.U.239.238; 3.U.239.239; 3.U.239.154; 3.U.239.157; 3.U.239.166; 3.U.239.169; 3.U.239.172; 3.U.239.175; 3.U.239.240; 3.U.239.244; 3.U.154.228; 3.U.154.229; 3.U.154.230; 3.U.154.231; 3.U.154.236; 3.U.154.237; 3.U.154.238; 3.U.154.239; 3.U.154.154; 3.U.154.157; 3.U.154.166; 3.U.154.169; 3.U.154.172; 3.U.154.175; 3.U.154.240; 3.U.154.244; 3.U.157.228; 3.U.157.229; 3.U.157.230; 3.U.157.231; 3.U.157.236; 3.U.157.237; 3.U.157.238; 3.U.157.239; 3.U.157.154; 3.U.157.157; 3.U.157.166; 3.U.157.169; 3.U.157.172; 3.U.157.175; 3.U.157.240; 3.U.157.244; 3.U.166.228; 3.U.166.229; 3.U.166.230; 3.U.166.231; 3.U.166.236; 3.U.166.237; 3.U.166.238; 3.U.166.239; 3.U.166.154; 3.U.166.157; 3.U.166.166; 3.U.166.169; 3.U.166.172; 3.U.166.175; 3.U.166.240; 3.U.166.244; 3.U.169.228; 3.U.169.229; 3.U.169.230; 3.U.169.231; 3.U.169.236; 3.U.169.237; 3.U.169.238; 3.U.169.239; 3.U.169.154; 3.U.169.157; 3.U.169.166; 3.U.169.169; 3.U.169.172; 3.U.169.175; 3.U.169.240; 3.U.169.244; 3.U.172.228; 3.U.172.229; 3.U.172.230; 3.U.172.231; 3.U.172.236; 3.U.172.237; 3.U.172.238; 3.U.172.239; 3.U.172.154; 3.U.172.157; 3.U.172.166; 3.U.172.169; 3.U.172.172; 3.U.172.175; 3.U.172.240; 3.U.172.244; 3.U.175.228; 3.U.175.229; 3.U.175.230; 3.U.175.231; 3.U.175.236; 3.U.175.237; 3.U.175.238; 3.U.175.239; 3.U.175.154; 3.U.175.157; 3.U.175.166; 3.U.175.169;

3.U.175.172; 3.U.175.175; 3.U.175.240; 3.U.175.244; 3.U.240.228; 3.U.240.229; 3.U.240.230; 3.U.240.231; 3.U.240.236; 3.U.240.237; 3.U.240.238; 3.U.240.239; 3.U.240.154; 3.U.240.157; 3.U.240.166; 3.U.240.169; 3.U.240.172; 3.U.240.175; 3.U.240.240; 3.U.240.244; 3.U.244.228; 3.U.244.229; 3.U.244.230; 3.U.244.231; 3.U.244.236; 3.U.244.237; 3.U.244.238; 3.U.244.239; 3.U.244.154; 3.U.244.157; 3.U.244.166; 3.U.244.169; 3.U.244.172; 3.U.244.175; 3.U.244.240; 3.U.244.244;

Prodrugs of 3.W

3.W.228.228; 3.W.228.229; 3.W.228.230; 3.W.228.231; 3.W.228.236; 3.W.228.237; 3.W.228.238; 3.W.228.239; 3.W.228.154; 3.W.228.157; 3.W.228.166; 3.W.228.169; 3.W.228.172; 3.W.228.175; 3.W.228.240; 3.W.228.244; 3.W.229.228; 3.W.229.229; 3.W.229.230; 3.W.229.231; 3.W.229.236; 3.W.229.237; 3.W.229.238; 3.W.229.239; 3.W.229.154; 3.W.229.157; 3.W.229.166; 3.W.229.169; 3.W.229.172; 3.W.229.175; 3.W.229.240; 3.W.229.244; 3.W.230.228; 3.W.230.229; 3.W.230.230; 3.W.230.231; 3.W.230.236; 3.W.230.237; 3.W.230.238; 3.W.230.239; 3.W.230.154; 3.W.230.157; 3.W.230.166; 3.W.230.169; 3.W.230.172; 3.W.230.175; 3.W.230.240; 3.W.230.244; 3.W.231.228; 3.W.231.229; 3.W.231.230; 3.W.231.231; 3.W.231.236; 3.W.231.237; 3.W.231.238; 3.W.231.239; 3.W.231.154; 3.W.231.157; 3.W.231.166; 3.W.231.169; 3.W.231.172; 3.W.231.175; 3.W.231.240; 3.W.231.244; 3.W.236.228; 3.W.236.229; 3.W.236.230; 3.W.236.231; 3.W.236.236; 3.W.236.237; 3.W.236.238; 3.W.236.239; 3.W.236.154; 3.W.236.157; 3.W.236.166; 3.W.236.169; 3.W.236.172; 3.W.236.175; 3.W.236.240; 3.W.236.244; 3.W.237.228; 3.W.237.229; 3.W.237.230; 3.W.237.231; 3.W.237.236; 3.W.237.237; 3.W.237.238; 3.W.237.239; 3.W.237.154; 3.W.237.157; 3.W.237.166; 3.W.237.169; 3.W.237.172; 3.W.237.175; 3.W.237.240; 3.W.237.244; 3.W.238.228; 3.W.238.229; 3.W.238.230; 3.W.238.231;

3.W.238.236; 3.W.238.237; 3.W.238.238; 3.W.238.239; 3.W.238.154; 3.W.238.157; 3.W.238.166; 3.W.238.169; 3.W.238.172; 3.W.238.175; 3.W.238.240; 3.W.238.244; 3.W.239.228; 3.W.239.229; 3.W.239.230; 3.W.239.231; 3.W.239.236; 3.W.239.237; 3.W.239.238; 3.W.239.239; 3.W.239.154; 3.W.239.157; 3.W.239.166; 3.W.239.169; 3.W.239.172; 3.W.239.175; 3.W.239.240; 3.W.239.244; 3.W.154.228; 3.W.154.229; 3.W.154.230; 3.W.154.231; 3.W.154.236; 3.W.154.237; 3.W.154.238; 3.W.154.239; 3.W.154.154; 3.W.154.157; 3.W.154.166; 3.W.154.169; 3.W.154.172; 3.W.154.175; 3.W.154.240; 3.W.154.244; 3.W.157.228; 3.W.157.229; 3.W.157.230; 3.W.157.231; 3.W.157.236; 3.W.157.237; 3.W.157.238; 3.W.157.239; 3.W.157.154; 3.W.157.157; 3.W.157.166; 3.W.157.169; 3.W.157.172; 3.W.157.175; 3.W.157.240; 3.W.157.244; 3.W.166.228; 3.W.166.229; 3.W.166.230; 3.W.166.231; 3.W.166.236; 3.W.166.237; 3.W.166.238; 3.W.166.239; 3.W.166.154; 3.W.166.157; 3.W.166.166; 3.W.166.169; 3.W.166.172; 3.W.166.175; 3.W.166.240; 3.W.166.244; 3.W.169.228; 3.W.169.229; 3.W.169.230; 3.W.169.231; 3.W.169.236; 3.W.169.237; 3.W.169.238; 3.W.169.239; 3.W.169.154; 3.W.169.157; 3.W.169.166; 3.W.169.169; 3.W.169.172; 3.W.169.175; 3.W.169.240; 3.W.169.244; 3.W.172.228; 3.W.172.229; 3.W.172.230; 3.W.172.231; 3.W.172.236; 3.W.172.237; 3.W.172.238; 3.W.172.239; 3.W.172.154; 3.W.172.157; 3.W.172.166; 3.W.172.169; 3.W.172.172; 3.W.172.175; 3.W.172.240; 3.W.172.244; 3.W.175.228; 3.W.175.229; 3.W.175.230; 3.W.175.231; 3.W.175.236; 3.W.175.237; 3.W.175.238; 3.W.175.239; 3.W.175.154; 3.W.175.157; 3.W.175.166; 3.W.175.169; 3.W.175.172; 3.W.175.175; 3.W.175.240; 3.W.175.244; 3.W.240.228; 3.W.240.229; 3.W.240.230; 3.W.240.231; 3.W.240.236; 3.W.240.237; 3.W.240.238; 3.W.240.239; 3.W.240.154; 3.W.240.157; 3.W.240.166; 3.W.240.169; 3.W.240.172; 3.W.240.175; 3.W.240.240; 3.W.240.244; 3.W.244.228; 3.W.244.229; 3.W.244.230; 3.W.244.231; 3.W.244.236; 3.W.244.237; 3.W.244.238; 3.W.244.239; 3.W.244.154; 3.W.244.157;

3.W.244.166; 3.W.244.169; 3.W.244.172; 3.W.244.175; 3.W.244.240; 3.W.244.244;

Prodrugs of 3.Y

3.Y.228.228; 3.Y.228.229; 3.Y.228.230; 3.Y.228.231; 3.Y.228.236; 3.Y.228.237; 3.Y.228.238; 3.Y.228.239; 3.Y.228.154; 3.Y.228.157; 3.Y.228.166; 3.Y.228.169; 3.Y.228.172; 3.Y.228.175; 3.Y.228.240; 3.Y.228.244; 3.Y.229.228; 3.Y.229.229; 3.Y.229.230; 3.Y.229.231; 3.Y.229.236; 3.Y.229.237; 3.Y.229.238; 3.Y.229.239; 3.Y.229.154; 3.Y.229.157; 3.Y.229.166; 3.Y.229.169; 3.Y.229.172; 3.Y.229.175; 3.Y.229.240; 3.Y.229.244; 3.Y.230.228; 3.Y.230.229; 3.Y.230.230; 3.Y.230.231; 3.Y.230.236; 3.Y.230.237; 3.Y.230.238; 3.Y.230.239; 3.Y.230.154; 3.Y.230.157; 3.Y.230.166; 3.Y.230.169; 3.Y.230.172; 3.Y.230.175; 3.Y.230.240; 3.Y.230.244; 3.Y.231.228; 3.Y.231.229; 3.Y.231.230; 3.Y.231.231; 3.Y.231.236; 3.Y.231.237; 3.Y.231.238; 3.Y.231.239; 3.Y.231.154; 3.Y.231.157; 3.Y.231.166; 3.Y.231.169; 3.Y.231.172; 3.Y.231.175; 3.Y.231.240; 3.Y.231.244; 3.Y.236.228; 3.Y.236.229; 3.Y.236.230; 3.Y.236.231; 3.Y.236.236; 3.Y.236.237; 3.Y.236.238; 3.Y.236.239; 3.Y.236.154; 3.Y.236.157; 3.Y.236.166; 3.Y.236.169; 3.Y.236.172; 3.Y.236.175; 3.Y.236.240; 3.Y.236.244; 3.Y.237.228; 3.Y.237.229; 3.Y.237.230; 3.Y.237.231; 3.Y.237.236; 3.Y.237.237; 3.Y.237.238; 3.Y.237.239; 3.Y.237.154; 3.Y.237.157; 3.Y.237.166; 3.Y.237.169; 3.Y.237.172; 3.Y.237.175; 3.Y.237.240; 3.Y.237.244; 3.Y.238.228; 3.Y.238.229; 3.Y.238.230; 3.Y.238.231; 3.Y.238.236; 3.Y.238.237; 3.Y.238.238; 3.Y.238.239; 3.Y.238.154; 3.Y.238.157; 3.Y.238.166; 3.Y.238.169; 3.Y.238.172; 3.Y.238.175; 3.Y.238.240; 3.Y.238.244; 3.Y.239.228; 3.Y.239.229; 3.Y.239.230; 3.Y.239.231; 3.Y.239.236; 3.Y.239.237; 3.Y.239.238; 3.Y.239.239; 3.Y.239.154; 3.Y.239.157; 3.Y.239.166; 3.Y.239.169; 3.Y.239.172; 3.Y.239.175; 3.Y.239.240; 3.Y.239.244; 3.Y.154.228; 3.Y.154.229; 3.Y.154.230; 3.Y.154.231; 3.Y.154.236; 3.Y.154.237; 3.Y.154.238; 3.Y.154.239; 3.Y.154.154; 3.Y.154.157; 3.Y.154.166; 3.Y.154.169; 3.Y.154.172; 3.Y.154.175; 3.Y.154.240; 3.Y.154.244; 3.Y.157.228; 3.Y.157.229; 3.Y.157.230; 3.Y.157.231; 3.Y.157.236; 3.Y.157.237; 3.Y.157.238; 3.Y.157.239; 3.Y.157.154; 3.Y.157.157; 3.Y.157.166;

3.Y.157.169; 3.Y.157.172; 3.Y.157.175; 3.Y.157.240; 3.Y.157.244; 3.Y.166.228; 3.Y.166.229; 3.Y.166.230; 3.Y.166.231; 3.Y.166.236; 3.Y.166.237; 3.Y.166.238; 3.Y.166.239; 3.Y.166.154; 3.Y.166.157; 3.Y.166.166; 3.Y.166.169; 3.Y.166.172; 3.Y.166.175; 3.Y.166.240; 3.Y.166.244; 3.Y.169.228; 3.Y.169.229; 3.Y.169.230; 3.Y.169.231; 3.Y.169.236; 3.Y.169.237; 3.Y.169.238; 3.Y.169.239; 3.Y.169.154; 3.Y.169.157; 3.Y.169.166; 3.Y.169.169; 3.Y.169.172; 3.Y.169.175; 3.Y.169.240; 3.Y.169.244; 3.Y.172.228; 3.Y.172.229; 3.Y.172.230; 3.Y.172.231; 3.Y.172.236; 3.Y.172.237; 3.Y.172.238; 3.Y.172.239; 3.Y.172.154; 3.Y.172.157; 3.Y.172.166; 3.Y.172.169; 3.Y.172.172; 3.Y.172.175; 3.Y.172.240; 3.Y.172.244; 3.Y.175.228; 3.Y.175.229; 3.Y.175.230; 3.Y.175.231; 3.Y.175.236; 3.Y.175.237; 3.Y.175.238; 3.Y.175.239; 3.Y.175.154; 3.Y.175.157; 3.Y.175.166; 3.Y.175.169; 3.Y.175.172; 3.Y.175.175; 3.Y.175.240; 3.Y.175.244; 3.Y.240.228; 3.Y.240.229; 3.Y.240.230; 3.Y.240.231; 3.Y.240.236; 3.Y.240.237; 3.Y.240.238; 3.Y.240.239; 3.Y.240.154; 3.Y.240.157; 3.Y.240.166; 3.Y.240.169; 3.Y.240.172; 3.Y.240.175; 3.Y.240.240; 3.Y.240.244; 3.Y.244.228; 3.Y.244.229; 3.Y.244.230; 3.Y.244.231; 3.Y.244.236; 3.Y.244.237; 3.Y.244.238; 3.Y.244.239; 3.Y.244.154; 3.Y.244.157; 3.Y.244.166; 3.Y.244.169; 3.Y.244.172; 3.Y.244.175; 3.Y.244.240; 3.Y.244.244;

Prodrugs of 4.B

4.B.228.228; 4.B.228.229; 4.B.228.230; 4.B.228.231; 4.B.228.236; 4.B.228.237; 4.B.228.238; 4.B.228.239; 4.B.228.154; 4.B.228.157; 4.B.228.166; 4.B.228.169; 4.B.228.172; 4.B.228.175; 4.B.228.240; 4.B.228.244; 4.B.229.228; 4.B.229.229; 4.B.229.230; 4.B.229.231; 4.B.229.236; 4.B.229.237; 4.B.229.238; 4.B.229.239; 4.B.229.154; 4.B.229.157; 4.B.229.166; 4.B.229.169; 4.B.229.172; 4.B.229.175; 4.B.229.240; 4.B.229.244; 4.B.230.228; 4.B.230.229; 4.B.230.230; 4.B.230.231; 4.B.230.236; 4.B.230.237; 4.B.230.238; 4.B.230.239; 4.B.230.154; 4.B.230.157; 4.B.230.166; 4.B.230.169; 4.B.230.172; 4.B.230.175; 4.B.230.240; 4.B.230.244; 4.B.231.228; 4.B.231.229; 4.B.231.230; 4.B.231.231; 4.B.231.236; 4.B.231.237; 4.B.231.238; 4.B.231.239; 4.B.231.154; 4.B.231.157; 4.B.231.166; 4.B.231.169; 4.B.231.172; 4.B.231.175; 4.B.231.240; 4.B.231.244; 4.B.236.228;

4.B.236.229; 4.B.236.230; 4.B.236.231; 4.B.236.236; 4.B.236.237; 4.B.236.238; 4.B.236.239; 4.B.236.154; 4.B.236.157; 4.B.236.166; 4.B.236.169; 4.B.236.172; 4.B.236.175; 4.B.236.240; 4.B.236.244; 4.B.237.228; 4.B.237.229; 4.B.237.230; 4.B.237.231; 4.B.237.236; 4.B.237.237; 4.B.237.238; 4.B.237.239; 4.B.237.154; 4.B.237.157; 4.B.237.166; 4.B.237.169; 4.B.237.172; 4.B.237.175; 4.B.237.240; 4.B.237.244; 4.B.238.228; 4.B.238.229; 4.B.238.230; 4.B.238.231; 4.B.238.236; 4.B.238.237; 4.B.238.238; 4.B.238.239; 4.B.238.154; 4.B.238.157; 4.B.238.166; 4.B.238.169; 4.B.238.172; 4.B.238.175; 4.B.238.240; 4.B.238.244; 4.B.239.228; 4.B.239.229; 4.B.239.230; 4.B.239.231; 4.B.239.236; 4.B.239.237; 4.B.239.238; 4.B.239.239; 4.B.239.154; 4.B.239.157; 4.B.239.166; 4.B.239.169; 4.B.239.172; 4.B.239.175; 4.B.239.240; 4.B.239.244; 4.B.154.228; 4.B.154.229; 4.B.154.230; 4.B.154.231; 4.B.154.236; 4.B.154.237; 4.B.154.238; 4.B.154.239; 4.B.154.154; 4.B.154.157; 4.B.154.166; 4.B.154.169; 4.B.154.172; 4.B.154.175; 4.B.154.240; 4.B.154.244; 4.B.157.228; 4.B.157.229; 4.B.157.230; 4.B.157.231; 4.B.157.236; 4.B.157.237; 4.B.157.238; 4.B.157.239; 4.B.157.154; 4.B.157.157; 4.B.157.166; 4.B.157.169; 4.B.157.172; 4.B.157.175; 4.B.157.240; 4.B.157.244; 4.B.166.228; 4.B.166.229; 4.B.166.230; 4.B.166.231; 4.B.166.236; 4.B.166.237; 4.B.166.238; 4.B.166.239; 4.B.166.154; 4.B.166.157; 4.B.166.166; 4.B.166.169; 4.B.166.172; 4.B.166.175; 4.B.166.240; 4.B.166.244; 4.B.169.228; 4.B.169.229; 4.B.169.230; 4.B.169.231; 4.B.169.236; 4.B.169.237; 4.B.169.238; 4.B.169.239; 4.B.169.154; 4.B.169.157; 4.B.169.166; 4.B.169.169; 4.B.169.172; 4.B.169.175; 4.B.169.240; 4.B.169.244; 4.B.172.228; 4.B.172.229; 4.B.172.230; 4.B.172.231; 4.B.172.236; 4.B.172.237; 4.B.172.238; 4.B.172.239; 4.B.172.154; 4.B.172.157; 4.B.172.166; 4.B.172.169; 4.B.172.172; 4.B.172.175; 4.B.172.240; 4.B.172.244; 4.B.175.228; 4.B.175.229; 4.B.175.230; 4.B.175.231; 4.B.175.236; 4.B.175.237; 4.B.175.238; 4.B.175.239; 4.B.175.154; 4.B.175.157; 4.B.175.166; 4.B.175.169; 4.B.175.172; 4.B.175.175; 4.B.175.240; 4.B.175.244; 4.B.240.228; 4.B.240.229; 4.B.240.230; 4.B.240.231; 4.B.240.236; 4.B.240.237; 4.B.240.238; 4.B.240.239; 4.B.240.154; 4.B.240.157; 4.B.240.166; 4.B.240.169; 4.B.240.172; 4.B.240.175; 4.B.240.240; 4.B.240.244; 4.B.244.228; 4.B.244.229; 4.B.244.230; 4.B.244.231; 4.B.244.236;

4.B.244.237; 4.B.244.238; 4.B.244.239; 4.B.244.154; 4.B.244.157; 4.B.244.166; 4.B.244.169; 4.B.244.172; 4.B.244.175; 4.B.244.240; 4.B.244.244;

Prodrugs of 4.D

4.D.228.228; 4.D.228.229; 4.D.228.230; 4.D.228.231; 4.D.228.236; 4.D.228.237; 4.D.228.238; 4.D.228.239; 4.D.228.154; 4.D.228.157; 4.D.228.166; 4.D.228.169; 4.D.228.172; 4.D.228.175; 4.D.228.240; 4.D.228.244; 4.D.229.228; 4.D.229.229; 4.D.229.230; 4.D.229.231; 4.D.229.236; 4.D.229.237; 4.D.229.238; 4.D.229.239; 4.D.229.154; 4.D.229.157; 4.D.229.166; 4.D.229.169; 4.D.229.172; 4.D.229.175; 4.D.229.240; 4.D.229.244; 4.D.230.228; 4.D.230.229; 4.D.230.230; 4.D.230.231; 4.D.230.236; 4.D.230.237; 4.D.230.238; 4.D.230.239; 4.D.230.154; 4.D.230.157; 4.D.230.166; 4.D.230.169; 4.D.230.172; 4.D.230.175; 4.D.230.240; 4.D.230.244; 4.D.231.228; 4.D.231.229; 4.D.231.230; 4.D.231.231; 4.D.231.236; 4.D.231.237; 4.D.231.238; 4.D.231.239; 4.D.231.154; 4.D.231.157; 4.D.231.166; 4.D.231.169; 4.D.231.172; 4.D.231.175; 4.D.231.240; 4.D.231.244; 4.D.236.228; 4.D.236.229; 4.D.236.230; 4.D.236.231; 4.D.236.236; 4.D.236.237; 4.D.236.238; 4.D.236.239; 4.D.236.154; 4.D.236.157; 4.D.236.166; 4.D.236.169; 4.D.236.172; 4.D.236.175; 4.D.236.240; 4.D.236.244; 4.D.237.228; 4.D.237.229; 4.D.237.230; 4.D.237.231; 4.D.237.236; 4.D.237.237; 4.D.237.238; 4.D.237.239; 4.D.237.154; 4.D.237.157; 4.D.237.166; 4.D.237.169; 4.D.237.172; 4.D.237.175; 4.D.237.240; 4.D.237.244; 4.D.238.228; 4.D.238.229; 4.D.238.230; 4.D.238.231; 4.D.238.236; 4.D.238.237; 4.D.238.238; 4.D.238.239; 4.D.238.154; 4.D.238.157; 4.D.238.166; 4.D.238.169; 4.D.238.172; 4.D.238.175; 4.D.238.240; 4.D.238.244; 4.D.239.228; 4.D.239.229; 4.D.239.230; 4.D.239.231; 4.D.239.236; 4.D.239.237; 4.D.239.238; 4.D.239.239; 4.D.239.154; 4.D.239.157; 4.D.239.166; 4.D.239.169; 4.D.239.172; 4.D.239.175; 4.D.239.240; 4.D.239.244; 4.D.154.228; 4.D.154.229;

4.D.154.230; 4.D.154.231; 4.D.154.236; 4.D.154.237; 4.D.154.238; 4.D.154.239; 4.D.154.154; 4.D.154.157; 4.D.154.166; 4.D.154.169; 4.D.154.172; 4.D.154.175; 4.D.154.240; 4.D.154.244; 4.D.157.228; 4.D.157.229; 4.D.157.230; 4.D.157.231; 4.D.157.236; 4.D.157.237; 4.D.157.238; 4.D.157.239; 4.D.157.154; 4.D.157.157; 4.D.157.166; 4.D.157.169; 4.D.157.172; 4.D.157.175; 4.D.157.240; 4.D.157.244; 4.D.166.228; 4.D.166.229; 4.D.166.230; 4.D.166.231; 4.D.166.236; 4.D.166.237; 4.D.166.238; 4.D.166.239; 4.D.166.154; 4.D.166.157; 4.D.166.166; 4.D.166.169; 4.D.166.172; 4.D.166.175; 4.D.166.240; 4.D.166.244; 4.D.169.228; 4.D.169.229; 4.D.169.230; 4.D.169.231; 4.D.169.236; 4.D.169.237; 4.D.169.238; 4.D.169.239; 4.D.169.154; 4.D.169.157; 4.D.169.166; 4.D.169.169; 4.D.169.172; 4.D.169.175; 4.D.169.240; 4.D.169.244; 4.D.172.228; 4.D.172.229; 4.D.172.230; 4.D.172.231; 4.D.172.236; 4.D.172.237; 4.D.172.238; 4.D.172.239; 4.D.172.154; 4.D.172.157; 4.D.172.166; 4.D.172.169; 4.D.172.172; 4.D.172.175; 4.D.172.240; 4.D.172.244; 4.D.175.228; 4.D.175.229; 4.D.175.230; 4.D.175.231; 4.D.175.236; 4.D.175.237; 4.D.175.238; 4.D.175.239; 4.D.175.154; 4.D.175.157; 4.D.175.166; 4.D.175.169; 4.D.175.172; 4.D.175.175; 4.D.175.240; 4.D.175.244; 4.D.240.228; 4.D.240.229; 4.D.240.230; 4.D.240.231; 4.D.240.236; 4.D.240.237; 4.D.240.238; 4.D.240.239; 4.D.240.154; 4.D.240.157; 4.D.240.166; 4.D.240.169; 4.D.240.172; 4.D.240.175; 4.D.240.240; 4.D.240.244; 4.D.244.228; 4.D.244.229; 4.D.244.230; 4.D.244.231; 4.D.244.236; 4.D.244.237; 4.D.244.238; 4.D.244.239; 4.D.244.154; 4.D.244.157; 4.D.244.166; 4.D.244.169; 4.D.244.172; 4.D.244.175; 4.D.244.240; 4.D.244.244;

Prodrugs of 4.E

4.E.228.228; 4.E.228.229; 4.E.228.230; 4.E.228.231; 4.E.228.236; 4.E.228.237; 4.E.228.238; 4.E.228.239; 4.E.228.154; 4.E.228.157; 4.E.228.166;

4.E.228.169; 4.E.228.172; 4.E.228.175; 4.E.228.240; 4.E.228.244; 4.E.229.228; 4.E.229.229; 4.E.229.230; 4.E.229.231; 4.E.229.236; 4.E.229.237; 4.E.229.238; 4.E.229.239; 4.E.229.154; 4.E.229.157; 4.E.229.166; 4.E.229.169; 4.E.229.172; 4.E.229.175; 4.E.229.240; 4.E.229.244; 4.E.230.228; 4.E.230.229; 4.E.230.230; 4.E.230.231; 4.E.230.236; 4.E.230.237; 4.E.230.238; 4.E.230.239; 4.E.230.154; 4.E.230.157; 4.E.230.166; 4.E.230.169; 4.E.230.172; 4.E.230.175; 4.E.230.240; 4.E.230.244; 4.E.231.228; 4.E.231.229; 4.E.231.230; 4.E.231.231; 4.E.231.236; 4.E.231.237; 4.E.231.238; 4.E.231.239; 4.E.231.154; 4.E.231.157; 4.E.231.166; 4.E.231.169; 4.E.231.172; 4.E.231.175; 4.E.231.240; 4.E.231.244; 4.E.236.228; 4.E.236.229; 4.E.236.230; 4.E.236.231; 4.E.236.236; 4.E.236.237; 4.E.236.238; 4.E.236.239; 4.E.236.154; 4.E.236.157; 4.E.236.166; 4.E.236.169; 4.E.236.172; 4.E.236.175; 4.E.236.240; 4.E.236.244; 4.E.237.228; 4.E.237.229; 4.E.237.230; 4.E.237.231; 4.E.237.236; 4.E.237.237; 4.E.237.238; 4.E.237.239; 4.E.237.154; 4.E.237.157; 4.E.237.166; 4.E.237.169; 4.E.237.172; 4.E.237.175; 4.E.237.240; 4.E.237.244; 4.E.238.228; 4.E.238.229; 4.E.238.230; 4.E.238.231; 4.E.238.236; 4.E.238.237; 4.E.238.238; 4.E.238.239; 4.E.238.154; 4.E.238.157; 4.E.238.166; 4.E.238.169; 4.E.238.172; 4.E.238.175; 4.E.238.240; 4.E.238.244; 4.E.239.228; 4.E.239.229; 4.E.239.230; 4.E.239.231; 4.E.239.236; 4.E.239.237; 4.E.239.238; 4.E.239.239; 4.E.239.154; 4.E.239.157; 4.E.239.166; 4.E.239.169; 4.E.239.172; 4.E.239.175; 4.E.239.240; 4.E.239.244; 4.E.154.228; 4.E.154.229; 4.E.154.230; 4.E.154.231; 4.E.154.236; 4.E.154.237; 4.E.154.238; 4.E.154.239; 4.E.154.154; 4.E.154.157; 4.E.154.166; 4.E.154.169; 4.E.154.172; 4.E.154.175; 4.E.154.240; 4.E.154.244; 4.E.157.228; 4.E.157.229; 4.E.157.230; 4.E.157.231; 4.E.157.236; 4.E.157.237; 4.E.157.238; 4.E.157.239; 4.E.157.154; 4.E.157.157; 4.E.157.166; 4.E.157.169; 4.E.157.172; 4.E.157.175; 4.E.157.240; 4.E.157.244; 4.E.166.228; 4.E.166.229; 4.E.166.230; 4.E.166.231; 4.E.166.236; 4.E.166.237; 4.E.166.238; 4.E.166.239; 4.E.166.154; 4.E.166.157; 4.E.166.166; 4.E.166.169; 4.E.166.172; 4.E.166.175; 4.E.166.240; 4.E.166.244; 4.E.169.228; 4.E.169.229; 4.E.169.230; 4.E.169.231; 4.E.169.236; 4.E.169.237; 4.E.169.238; 4.E.169.239; 4.E.169.154; 4.E.169.157; 4.E.169.166; 4.E.169.169; 4.E.169.172; 4.E.169.175; 4.E.169.240;

4.E.169.244; 4.E.172.228; 4.E.172.229; 4.E.172.230; 4.E.172.231; 4.E.172.236; 4.E.172.237; 4.E.172.238; 4.E.172.239; 4.E.172.154; 4.E.172.157; 4.E.172.166; 4.E.172.169; 4.E.172.172; 4.E.172.175; 4.E.172.240; 4.E.172.244; 4.E.175.228; 4.E.175.229; 4.E.175.230; 4.E.175.231; 4.E.175.236; 4.E.175.237; 4.E.175.238; 4.E.175.239; 4.E.175.154; 4.E.175.157; 4.E.175.166; 4.E.175.169; 4.E.175.172; 4.E.175.175; 4.E.175.240; 4.E.175.244; 4.E.240.228; 4.E.240.229; 4.E.240.230; 4.E.240.231; 4.E.240.236; 4.E.240.237; 4.E.240.238; 4.E.240.239; 4.E.240.154; 4.E.240.157; 4.E.240.166; 4.E.240.169; 4.E.240.172; 4.E.240.175; 4.E.240.240; 4.E.240.244; 4.E.244.228; 4.E.244.229; 4.E.244.230; 4.E.244.231; 4.E.244.236; 4.E.244.237; 4.E.244.238; 4.E.244.239; 4.E.244.154; 4.E.244.157; 4.E.244.166; 4.E.244.169; 4.E.244.172; 4.E.244.175; 4.E.244.240; 4.E.244.244;

Prodrugs of 4.G

4.G.228.228; 4.G.228.229; 4.G.228.230; 4.G.228.231; 4.G.228.236; 4.G.228.237; 4.G.228.238; 4.G.228.239; 4.G.228.154; 4.G.228.157; 4.G.228.166; 4.G.228.169; 4.G.228.172; 4.G.228.175; 4.G.228.240; 4.G.228.244; 4.G.229.228; 4.G.229.229; 4.G.229.230; 4.G.229.231; 4.G.229.236; 4.G.229.237; 4.G.229.238; 4.G.229.239; 4.G.229.154; 4.G.229.157; 4.G.229.166; 4.G.229.169; 4.G.229.172; 4.G.229.175; 4.G.229.240; 4.G.229.244; 4.G.230.228; 4.G.230.229; 4.G.230.230; 4.G.230.231; 4.G.230.236; 4.G.230.237; 4.G.230.238; 4.G.230.239; 4.G.230.154; 4.G.230.157; 4.G.230.166; 4.G.230.169; 4.G.230.172; 4.G.230.175; 4.G.230.240; 4.G.230.244; 4.G.231.228; 4.G.231.229; 4.G.231.230; 4.G.231.231; 4.G.231.236; 4.G.231.237; 4.G.231.238; 4.G.231.239; 4.G.231.154; 4.G.231.157; 4.G.231.166; 4.G.231.169; 4.G.231.172; 4.G.231.175; 4.G.231.240; 4.G.231.244; 4.G.236.228; 4.G.236.229; 4.G.236.230; 4.G.236.231; 4.G.236.236; 4.G.236.237; 4.G.236.238; 4.G.236.239; 4.G.236.154; 4.G.236.157; 4.G.236.166; 4.G.236.169; 4.G.236.172; 4.G.236.175; 4.G.236.240; 4.G.236.244; 4.G.237.228; 4.G.237.229; 4.G.237.230; 4.G.237.231; 4.G.237.236;

4.G.237.237; 4.G.237.238; 4.G.237.239; 4.G.237.154; 4.G.237.157; 4.G.237.166; 4.G.237.169; 4.G.237.172; 4.G.237.175; 4.G.237.240; 4.G.237.244; 4.G.238.228; 4.G.238.229; 4.G.238.230; 4.G.238.231; 4.G.238.236; 4.G.238.237; 4.G.238.238; 4.G.238.239; 4.G.238.154; 4.G.238.157; 4.G.238.166; 4.G.238.169; 4.G.238.172; 4.G.238.175; 4.G.238.240; 4.G.238.244; 4.G.239.228; 4.G.239.229; 4.G.239.230; 4.G.239.231; 4.G.239.236; 4.G.239.237; 4.G.239.238; 4.G.239.239; 4.G.239.154; 4.G.239.157; 4.G.239.166; 4.G.239.169; 4.G.239.172; 4.G.239.175; 4.G.239.240; 4.G.239.244; 4.G.154.228; 4.G.154.229; 4.G.154.230; 4.G.154.231; 4.G.154.236; 4.G.154.237; 4.G.154.238; 4.G.154.239; 4.G.154.154; 4.G.154.157; 4.G.154.166; 4.G.154.169; 4.G.154.172; 4.G.154.175; 4.G.154.240; 4.G.154.244; 4.G.157.228; 4.G.157.229; 4.G.157.230; 4.G.157.231; 4.G.157.236; 4.G.157.237; 4.G.157.238; 4.G.157.239; 4.G.157.154; 4.G.157.157; 4.G.157.166; 4.G.157.169; 4.G.157.172; 4.G.157.175; 4.G.157.240; 4.G.157.244; 4.G.166.228; 4.G.166.229; 4.G.166.230; 4.G.166.231; 4.G.166.236; 4.G.166.237; 4.G.166.238; 4.G.166.239; 4.G.166.154; 4.G.166.157; 4.G.166.166; 4.G.166.169; 4.G.166.172; 4.G.166.175; 4.G.166.240; 4.G.166.244; 4.G.169.228; 4.G.169.229; 4.G.169.230; 4.G.169.231; 4.G.169.236; 4.G.169.237; 4.G.169.238; 4.G.169.239; 4.G.169.154; 4.G.169.157; 4.G.169.166; 4.G.169.169; 4.G.169.172; 4.G.169.175; 4.G.169.240; 4.G.169.244; 4.G.172.228; 4.G.172.229; 4.G.172.230; 4.G.172.231; 4.G.172.236; 4.G.172.237; 4.G.172.238; 4.G.172.239; 4.G.172.154; 4.G.172.157; 4.G.172.166; 4.G.172.169; 4.G.172.172; 4.G.172.175; 4.G.172.240; 4.G.172.244; 4.G.175.228; 4.G.175.229; 4.G.175.230; 4.G.175.231; 4.G.175.236; 4.G.175.237; 4.G.175.238; 4.G.175.239; 4.G.175.154; 4.G.175.157; 4.G.175.166; 4.G.175.169; 4.G.175.172; 4.G.175.175; 4.G.175.240; 4.G.175.244; 4.G.240.228; 4.G.240.229; 4.G.240.230; 4.G.240.231; 4.G.240.236; 4.G.240.237; 4.G.240.238; 4.G.240.239; 4.G.240.154; 4.G.240.157; 4.G.240.166;

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Prodrugs of 4.I

4.I.228.228; 4.I.228.229; 4.I.228.230; 4.I.228.231; 4.I.228.236; 4.I.228.237; 4.I.228.238; 4.I.228.239; 4.I.228.154; 4.I.228.157; 4.I.228.166; 4.I.228.169; 4.I.228.172; 4.I.228.175; 4.I.228.240; 4.I.228.244; 4.I.229.228; 4.I.229.229; 4.I.229.230; 4.I.229.231; 4.I.229.236; 4.I.229.237; 4.I.229.238; 4.I.229.239; 4.I.229.154; 4.I.229.157; 4.I.229.166; 4.I.229.169; 4.I.229.172; 4.I.229.175; 4.I.229.240; 4.I.229.244; 4.I.230.228; 4.I.230.229; 4.I.230.230; 4.I.230.231; 4.I.230.236; 4.I.230.237; 4.I.230.238; 4.I.230.239; 4.I.230.154; 4.I.230.157; 4.I.230.166; 4.I.230.169; 4.I.230.172; 4.I.230.175; 4.I.230.240; 4.I.230.244; 4.I.231.228; 4.I.231.229; 4.I.231.230; 4.I.231.231; 4.I.231.236; 4.I.231.237; 4.I.231.238; 4.I.231.239; 4.I.231.154; 4.I.231.157; 4.I.231.166; 4.I.231.169; 4.I.231.172; 4.I.231.175; 4.I.231.240; 4.I.231.244; 4.I.236.228; 4.I.236.229; 4.I.236.230; 4.I.236.231; 4.I.236.236; 4.I.236.237; 4.I.236.238; 4.I.236.239; 4.I.236.154; 4.I.236.157; 4.I.236.166; 4.I.236.169; 4.I.236.172; 4.I.236.175; 4.I.236.240; 4.I.236.244; 4.I.237.228; 4.I.237.229; 4.I.237.230; 4.I.237.231; 4.I.237.236; 4.I.237.237; 4.I.237.238; 4.I.237.239; 4.I.237.154; 4.I.237.157; 4.I.237.166; 4.I.237.169; 4.I.237.172; 4.I.237.175; 4.I.237.240; 4.I.237.244; 4.I.238.228; 4.I.238.229; 4.I.238.230; 4.I.238.231; 4.I.238.236; 4.I.238.237; 4.I.238.238; 4.I.238.239; 4.I.238.154; 4.I.238.157; 4.I.238.166; 4.I.238.169; 4.I.238.172; 4.I.238.175; 4.I.238.240; 4.I.238.244; 4.I.239.228; 4.I.239.229; 4.I.239.230; 4.I.239.231; 4.I.239.236; 4.I.239.237; 4.I.239.238; 4.I.239.239; 4.I.239.154; 4.I.239.157; 4.I.239.166; 4.I.239.169; 4.I.239.172; 4.I.239.175; 4.I.239.240; 4.I.239.244; 4.I.154.228; 4.I.154.229; 4.I.154.230; 4.I.154.231; 4.I.154.236; 4.I.154.237; 4.I.154.238; 4.I.154.239; 4.I.154.154; 4.I.154.157;

4.I.154.166; 4.I.154.169; 4.I.154.172; 4.I.154.175; 4.I.154.240; 4.I.154.244; 4.I.157.228; 4.I.157.229; 4.I.157.230; 4.I.157.231; 4.I.157.236; 4.I.157.237; 4.I.157.238; 4.I.157.239; 4.I.157.154; 4.I.157.157; 4.I.157.166; 4.I.157.169; 4.I.157.172; 4.I.157.175; 4.I.157.240; 4.I.157.244; 4.I.166.228; 4.I.166.229; 4.I.166.230; 4.I.166.231; 4.I.166.236; 4.I.166.237; 4.I.166.238; 4.I.166.239; 4.I.166.154; 4.I.166.157; 4.I.166.166; 4.I.166.169; 4.I.166.172; 4.I.166.175; 4.I.166.240; 4.I.166.244; 4.I.169.228; 4.I.169.229; 4.I.169.230; 4.I.169.231; 4.I.169.236; 4.I.169.237; 4.I.169.238; 4.I.169.239; 4.I.169.154; 4.I.169.157; 4.I.169.166; 4.I.169.169; 4.I.169.172; 4.I.169.175; 4.I.169.240; 4.I.169.244; 4.I.172.228; 4.I.172.229; 4.I.172.230; 4.I.172.231; 4.I.172.236; 4.I.172.237; 4.I.172.238; 4.I.172.239; 4.I.172.154; 4.I.172.157; 4.I.172.166; 4.I.172.169; 4.I.172.172; 4.I.172.175; 4.I.172.240; 4.I.172.244; 4.I.175.228; 4.I.175.229; 4.I.175.230; 4.I.175.231; 4.I.175.236; 4.I.175.237; 4.I.175.238; 4.I.175.239; 4.I.175.154; 4.I.175.157; 4.I.175.166; 4.I.175.169; 4.I.175.172; 4.I.175.175; 4.I.175.240; 4.I.175.244; 4.I.240.228; 4.I.240.229; 4.I.240.230; 4.I.240.231; 4.I.240.236; 4.I.240.237; 4.I.240.238; 4.I.240.239; 4.I.240.154; 4.I.240.157; 4.I.240.166; 4.I.240.169; 4.I.240.172; 4.I.240.175; 4.I.240.240; 4.I.240.244; 4.I.244.228; 4.I.244.229; 4.I.244.230; 4.I.244.231; 4.I.244.236; 4.I.244.237; 4.I.244.238; 4.I.244.239; 4.I.244.154; 4.I.244.157; 4.I.244.166; 4.I.244.169; 4.I.244.172; 4.I.244.175; 4.I.244.240; 4.I.244.244;

Prodrugs of 4.J

4.J.228.228; 4.J.228.229; 4.J.228.230; 4.J.228.231; 4.J.228.236; 4.J.228.237; 4.J.228.238; 4.J.228.239; 4.J.228.154; 4.J.228.157; 4.J.228.166; 4.J.228.169; 4.J.228.172; 4.J.228.175; 4.J.228.240; 4.J.228.244; 4.J.229.228; 4.J.229.229; 4.J.229.230; 4.J.229.231; 4.J.229.236; 4.J.229.237; 4.J.229.238; 4.J.229.239; 4.J.229.154; 4.J.229.157; 4.J.229.166; 4.J.229.169; 4.J.229.172; 4.J.229.175; 4.J.229.240; 4.J.229.244; 4.J.230.228; 4.J.230.229; 4.J.230.230; 4.J.230.231; 4.J.230.236; 4.J.230.237; 4.J.230.238; 4.J.230.239; 4.J.230.154; 4.J.230.157; 4.J.230.166; 4.J.230.169; 4.J.230.172; 4.J.230.175; 4.J.230.240; 4.J.230.244;

4.J.231.228; 4.J.231.229; 4.J.231.230; 4.J.231.231; 4.J.231.236; 4.J.231.237; 4.J.231.238; 4.J.231.239; 4.J.231.154; 4.J.231.157; 4.J.231.166; 4.J.231.169; 4.J.231.172; 4.J.231.175; 4.J.231.240; 4.J.231.244; 4.J.236.228; 4.J.236.229; 4.J.236.230; 4.J.236.231; 4.J.236.236; 4.J.236.237; 4.J.236.238; 4.J.236.239; 4.J.236.154; 4.J.236.157; 4.J.236.166; 4.J.236.169; 4.J.236.172; 4.J.236.175; 4.J.236.240; 4.J.236.244; 4.J.237.228; 4.J.237.229; 4.J.237.230; 4.J.237.231; 4.J.237.236; 4.J.237.237; 4.J.237.238; 4.J.237.239; 4.J.237.154; 4.J.237.157; 4.J.237.166; 4.J.237.169; 4.J.237.172; 4.J.237.175; 4.J.237.240; 4.J.237.244; 4.J.238.228; 4.J.238.229; 4.J.238.230; 4.J.238.231; 4.J.238.236; 4.J.238.237; 4.J.238.238; 4.J.238.239; 4.J.238.154; 4.J.238.157; 4.J.238.166; 4.J.238.169; 4.J.238.172; 4.J.238.175; 4.J.238.240; 4.J.238.244; 4.J.239.228; 4.J.239.229; 4.J.239.230; 4.J.239.231; 4.J.239.236; 4.J.239.237; 4.J.239.238; 4.J.239.239; 4.J.239.154; 4.J.239.157; 4.J.239.166; 4.J.239.169; 4.J.239.172; 4.J.239.175; 4.J.239.240; 4.J.239.244; 4.J.154.228; 4.J.154.229; 4.J.154.230; 4.J.154.231; 4.J.154.236; 4.J.154.237; 4.J.154.238; 4.J.154.239; 4.J.154.154; 4.J.154.157; 4.J.154.166; 4.J.154.169; 4.J.154.172; 4.J.154.175; 4.J.154.240; 4.J.154.244; 4.J.157.228; 4.J.157.229; 4.J.157.230; 4.J.157.231; 4.J.157.236; 4.J.157.237; 4.J.157.238; 4.J.157.239; 4.J.157.154; 4.J.157.157; 4.J.157.166; 4.J.157.169; 4.J.157.172; 4.J.157.175; 4.J.157.240; 4.J.157.244; 4.J.166.228; 4.J.166.229; 4.J.166.230; 4.J.166.231; 4.J.166.236; 4.J.166.237; 4.J.166.238; 4.J.166.239; 4.J.166.154; 4.J.166.157; 4.J.166.166; 4.J.166.169; 4.J.166.172; 4.J.166.175; 4.J.166.240; 4.J.166.244; 4.J.169.228; 4.J.169.229; 4.J.169.230; 4.J.169.231; 4.J.169.236; 4.J.169.237; 4.J.169.238; 4.J.169.239; 4.J.169.154; 4.J.169.157; 4.J.169.166; 4.J.169.169; 4.J.169.172; 4.J.169.175; 4.J.169.240; 4.J.169.244; 4.J.172.228; 4.J.172.229; 4.J.172.230; 4.J.172.231; 4.J.172.236; 4.J.172.237; 4.J.172.238; 4.J.172.239; 4.J.172.154; 4.J.172.157; 4.J.172.166; 4.J.172.169; 4.J.172.172; 4.J.172.175; 4.J.172.240; 4.J.172.244; 4.J.175.228; 4.J.175.229; 4.J.175.230; 4.J.175.231; 4.J.175.236; 4.J.175.237; 4.J.175.238; 4.J.175.239; 4.J.175.154; 4.J.175.157; 4.J.175.166; 4.J.175.169; 4.J.175.172; 4.J.175.175; 4.J.175.240; 4.J.175.244; 4.J.240.228; 4.J.240.229; 4.J.240.230; 4.J.240.231;

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Prodrugs of 4.L

4.L.228.228; 4.L.228.229; 4.L.228.230; 4.L.228.231; 4.L.228.236; 4.L.228.237; 4.L.228.238; 4.L.228.239; 4.L.228.154; 4.L.228.157; 4.L.228.166; 4.L.228.169; 4.L.228.172; 4.L.228.175; 4.L.228.240; 4.L.228.244; 4.L.229.228; 4.L.229.229; 4.L.229.230; 4.L.229.231; 4.L.229.236; 4.L.229.237; 4.L.229.238; 4.L.229.239; 4.L.229.154; 4.L.229.157; 4.L.229.166; 4.L.229.169; 4.L.229.172; 4.L.229.175; 4.L.229.240; 4.L.229.244; 4.L.230.228; 4.L.230.229; 4.L.230.230; 4.L.230.231; 4.L.230.236; 4.L.230.237; 4.L.230.238; 4.L.230.239; 4.L.230.154; 4.L.230.157; 4.L.230.166; 4.L.230.169; 4.L.230.172; 4.L.230.175; 4.L.230.240; 4.L.230.244; 4.L.231.228; 4.L.231.229; 4.L.231.230; 4.L.231.231; 4.L.231.236; 4.L.231.237; 4.L.231.238; 4.L.231.239; 4.L.231.154; 4.L.231.157; 4.L.231.166; 4.L.231.169; 4.L.231.172; 4.L.231.175; 4.L.231.240; 4.L.231.244; 4.L.236.228; 4.L.236.229; 4.L.236.230; 4.L.236.231; 4.L.236.236; 4.L.236.237; 4.L.236.238; 4.L.236.239; 4.L.236.154; 4.L.236.157; 4.L.236.166; 4.L.236.169; 4.L.236.172; 4.L.236.175; 4.L.236.240; 4.L.236.244; 4.L.237.228; 4.L.237.229; 4.L.237.230; 4.L.237.231; 4.L.237.236; 4.L.237.237; 4.L.237.238; 4.L.237.239; 4.L.237.154; 4.L.237.157; 4.L.237.166; 4.L.237.169; 4.L.237.172; 4.L.237.175; 4.L.237.240; 4.L.237.244; 4.L.238.228; 4.L.238.229; 4.L.238.230; 4.L.238.231; 4.L.238.236; 4.L.238.237; 4.L.238.238; 4.L.238.239; 4.L.238.154; 4.L.238.157; 4.L.238.166; 4.L.238.169; 4.L.238.172; 4.L.238.175; 4.L.238.240; 4.L.238.244; 4.L.239.228; 4.L.239.229; 4.L.239.230; 4.L.239.231; 4.L.239.236; 4.L.239.237; 4.L.239.238; 4.L.239.239; 4.L.239.154; 4.L.239.157; 4.L.239.166; 4.L.239.169; 4.L.239.172; 4.L.239.175; 4.L.239.240; 4.L.239.244; 4.L.154.228; 4.L.154.229; 4.L.154.230; 4.L.154.231; 4.L.154.236; 4.L.154.237; 4.L.154.238; 4.L.154.239; 4.L.154.154;

4.L.154.157; 4.L.154.166; 4.L.154.169; 4.L.154.172; 4.L.154.175; 4.L.154.240; 4.L.154.244; 4.L.157.228; 4.L.157.229; 4.L.157.230; 4.L.157.231; 4.L.157.236; 4.L.157.237; 4.L.157.238; 4.L.157.239; 4.L.157.154; 4.L.157.157; 4.L.157.166; 4.L.157.169; 4.L.157.172; 4.L.157.175; 4.L.157.240; 4.L.157.244; 4.L.166.228; 4.L.166.229; 4.L.166.230; 4.L.166.231; 4.L.166.236; 4.L.166.237; 4.L.166.238; 4.L.166.239; 4.L.166.154; 4.L.166.157; 4.L.166.166; 4.L.166.169; 4.L.166.172; 4.L.166.175; 4.L.166.240; 4.L.166.244; 4.L.169.228; 4.L.169.229; 4.L.169.230; 4.L.169.231; 4.L.169.236; 4.L.169.237; 4.L.169.238; 4.L.169.239; 4.L.169.154; 4.L.169.157; 4.L.169.166; 4.L.169.169; 4.L.169.172; 4.L.169.175; 4.L.169.240; 4.L.169.244; 4.L.172.228; 4.L.172.229; 4.L.172.230; 4.L.172.231; 4.L.172.236; 4.L.172.237; 4.L.172.238; 4.L.172.239; 4.L.172.154; 4.L.172.157; 4.L.172.166; 4.L.172.169; 4.L.172.172; 4.L.172.175; 4.L.172.240; 4.L.172.244; 4.L.175.228; 4.L.175.229; 4.L.175.230; 4.L.175.231; 4.L.175.236; 4.L.175.237; 4.L.175.238; 4.L.175.239; 4.L.175.154; 4.L.175.157; 4.L.175.166; 4.L.175.169; 4.L.175.172; 4.L.175.175; 4.L.175.240; 4.L.175.244; 4.L.240.228; 4.L.240.229; 4.L.240.230; 4.L.240.231; 4.L.240.236; 4.L.240.237; 4.L.240.238; 4.L.240.239; 4.L.240.154; 4.L.240.157; 4.L.240.166; 4.L.240.169; 4.L.240.172; 4.L.240.175; 4.L.240.240; 4.L.240.244; 4.L.244.228; 4.L.244.229; 4.L.244.230; 4.L.244.231; 4.L.244.236; 4.L.244.237; 4.L.244.238; 4.L.244.239; 4.L.244.154; 4.L.244.157; 4.L.244.166; 4.L.244.169; 4.L.244.172; 4.L.244.175; 4.L.244.240; 4.L.244.244;

Prodrugs of 4.O

4.O.228.228; 4.O.228.229; 4.O.228.230; 4.O.228.231; 4.O.228.236; 4.O.228.237; 4.O.228.238; 4.O.228.239; 4.O.228.154; 4.O.228.157; 4.O.228.166; 4.O.228.169; 4.O.228.172; 4.O.228.175; 4.O.228.240; 4.O.228.244; 4.O.229.228; 4.O.229.229; 4.O.229.230; 4.O.229.231; 4.O.229.236; 4.O.229.237; 4.O.229.238; 4.O.229.239; 4.O.229.154; 4.O.229.157; 4.O.229.166; 4.O.229.169; 4.O.229.172; 4.O.229.175; 4.O.229.240; 4.O.229.244; 4.O.230.228; 4.O.230.229; 4.O.230.230; 4.O.230.231; 4.O.230.236; 4.O.230.237; 4.O.230.238; 4.O.230.239;

4.O.230.154; 4.O.230.157; 4.O.230.166; 4.O.230.169; 4.O.230.172; 4.O.230.175; 4.O.230.240; 4.O.230.244; 4.O.231.228; 4.O.231.229; 4.O.231.230; 4.O.231.231; 4.O.231.236; 4.O.231.237; 4.O.231.238; 4.O.231.239; 4.O.231.154; 4.O.231.157; 4.O.231.166; 4.O.231.169; 4.O.231.172; 4.O.231.175; 4.O.231.240; 4.O.231.244; 4.O.236.228; 4.O.236.229; 4.O.236.230; 4.O.236.231; 4.O.236.236; 4.O.236.237; 4.O.236.238; 4.O.236.239; 4.O.236.154; 4.O.236.157; 4.O.236.166; 4.O.236.169; 4.O.236.172; 4.O.236.175; 4.O.236.240; 4.O.236.244; 4.O.237.228; 4.O.237.229; 4.O.237.230; 4.O.237.231; 4.O.237.236; 4.O.237.237; 4.O.237.238; 4.O.237.239; 4.O.237.154; 4.O.237.157; 4.O.237.166; 4.O.237.169; 4.O.237.172; 4.O.237.175; 4.O.237.240; 4.O.237.244; 4.O.238.228; 4.O.238.229; 4.O.238.230; 4.O.238.231; 4.O.238.236; 4.O.238.237; 4.O.238.238; 4.O.238.239; 4.O.238.154; 4.O.238.157; 4.O.238.166; 4.O.238.169; 4.O.238.172; 4.O.238.175; 4.O.238.240; 4.O.238.244; 4.O.239.228; 4.O.239.229; 4.O.239.230; 4.O.239.231; 4.O.239.236; 4.O.239.237; 4.O.239.238; 4.O.239.239; 4.O.239.154; 4.O.239.157; 4.O.239.166; 4.O.239.169; 4.O.239.172; 4.O.239.175; 4.O.239.240; 4.O.239.244; 4.O.154.228; 4.O.154.229; 4.O.154.230; 4.O.154.231; 4.O.154.236; 4.O.154.237; 4.O.154.238; 4.O.154.239; 4.O.154.154; 4.O.154.157; 4.O.154.166; 4.O.154.169; 4.O.154.172; 4.O.154.175; 4.O.154.240; 4.O.154.244; 4.O.157.228; 4.O.157.229; 4.O.157.230; 4.O.157.231; 4.O.157.236; 4.O.157.237; 4.O.157.238; 4.O.157.239; 4.O.157.154; 4.O.157.157; 4.O.157.166; 4.O.157.169; 4.O.157.172; 4.O.157.175; 4.O.157.240; 4.O.157.244; 4.O.166.228; 4.O.166.229; 4.O.166.230; 4.O.166.231; 4.O.166.236; 4.O.166.237; 4.O.166.238; 4.O.166.239; 4.O.166.154; 4.O.166.157; 4.O.166.166; 4.O.166.169; 4.O.166.172; 4.O.166.175; 4.O.166.240; 4.O.166.244; 4.O.169.228; 4.O.169.229; 4.O.169.230; 4.O.169.231; 4.O.169.236; 4.O.169.237; 4.O.169.238; 4.O.169.239; 4.O.169.154; 4.O.169.157; 4.O.169.166; 4.O.169.169; 4.O.169.172; 4.O.169.175;

4.O.169.240; 4.O.169.244; 4.O.172.228; 4.O.172.229; 4.O.172.230; 4.O.172.231; 4.O.172.236; 4.O.172.237; 4.O.172.238; 4.O.172.239; 4.O.172.154; 4.O.172.157; 4.O.172.166; 4.O.172.169; 4.O.172.172; 4.O.172.175; 4.O.172.240; 4.O.172.244; 4.O.175.228; 4.O.175.229; 4.O.175.230; 4.O.175.231; 4.O.175.236; 4.O.175.237; 4.O.175.238; 4.O.175.239; 4.O.175.154; 4.O.175.157; 4.O.175.166; 4.O.175.169; 4.O.175.172; 4.O.175.175; 4.O.175.240; 4.O.175.244; 4.O.240.228; 4.O.240.229; 4.O.240.230; 4.O.240.231; 4.O.240.236; 4.O.240.237; 4.O.240.238; 4.O.240.239; 4.O.240.154; 4.O.240.157; 4.O.240.166; 4.O.240.169; 4.O.240.172; 4.O.240.175; 4.O.240.240; 4.O.240.244; 4.O.244.228; 4.O.244.229; 4.O.244.230; 4.O.244.231; 4.O.244.236; 4.O.244.237; 4.O.244.238; 4.O.244.239; 4.O.244.154; 4.O.244.157; 4.O.244.166; 4.O.244.169; 4.O.244.172; 4.O.244.175; 4.O.244.240; 4.O.244.244;

Prodrugs of 4.P

4.P.228.228; 4.P.228.229; 4.P.228.230; 4.P.228.231; 4.P.228.236; 4.P.228.237; 4.P.228.238; 4.P.228.239; 4.P.228.154; 4.P.228.157; 4.P.228.166; 4.P.228.169; 4.P.228.172; 4.P.228.175; 4.P.228.240; 4.P.228.244; 4.P.229.228; 4.P.229.229; 4.P.229.230; 4.P.229.231; 4.P.229.236; 4.P.229.237; 4.P.229.238; 4.P.229.239; 4.P.229.154; 4.P.229.157; 4.P.229.166; 4.P.229.169; 4.P.229.172; 4.P.229.175; 4.P.229.240; 4.P.229.244; 4.P.230.228; 4.P.230.229; 4.P.230.230; 4.P.230.231; 4.P.230.236; 4.P.230.237; 4.P.230.238; 4.P.230.239; 4.P.230.154; 4.P.230.157; 4.P.230.166; 4.P.230.169; 4.P.230.172; 4.P.230.175; 4.P.230.240; 4.P.230.244; 4.P.231.228; 4.P.231.229; 4.P.231.230; 4.P.231.231; 4.P.231.236; 4.P.231.237; 4.P.231.238; 4.P.231.239; 4.P.231.154; 4.P.231.157; 4.P.231.166; 4.P.231.169; 4.P.231.172; 4.P.231.175; 4.P.231.240; 4.P.231.244; 4.P.236.228; 4.P.236.229; 4.P.236.230; 4.P.236.231; 4.P.236.236; 4.P.236.237; 4.P.236.238; 4.P.236.239; 4.P.236.154; 4.P.236.157; 4.P.236.166; 4.P.236.169; 4.P.236.172; 4.P.236.175; 4.P.236.240; 4.P.236.244; 4.P.237.228; 4.P.237.229; 4.P.237.230;

4.P.237.231; 4.P.237.236; 4.P.237.237; 4.P.237.238; 4.P.237.239; 4.P.237.154; 4.P.237.157; 4.P.237.166; 4.P.237.169; 4.P.237.172; 4.P.237.175; 4.P.237.240; 4.P.237.244; 4.P.238.228; 4.P.238.229; 4.P.238.230; 4.P.238.231; 4.P.238.236; 4.P.238.237; 4.P.238.238; 4.P.238.239; 4.P.238.154; 4.P.238.157; 4.P.238.166; 4.P.238.169; 4.P.238.172; 4.P.238.175; 4.P.238.240; 4.P.238.244; 4.P.239.228; 4.P.239.229; 4.P.239.230; 4.P.239.231; 4.P.239.236; 4.P.239.237; 4.P.239.238; 4.P.239.239; 4.P.239.154; 4.P.239.157; 4.P.239.166; 4.P.239.169; 4.P.239.172; 4.P.239.175; 4.P.239.240; 4.P.239.244; 4.P.154.228; 4.P.154.229; 4.P.154.230; 4.P.154.231; 4.P.154.236; 4.P.154.237; 4.P.154.238; 4.P.154.239; 4.P.154.154; 4.P.154.157; 4.P.154.166; 4.P.154.169; 4.P.154.172; 4.P.154.175; 4.P.154.240; 4.P.154.244; 4.P.157.228; 4.P.157.229; 4.P.157.230; 4.P.157.231; 4.P.157.236; 4.P.157.237; 4.P.157.238; 4.P.157.239; 4.P.157.154; 4.P.157.157; 4.P.157.166; 4.P.157.169; 4.P.157.172; 4.P.157.175; 4.P.157.240; 4.P.157.244; 4.P.166.228; 4.P.166.229; 4.P.166.230; 4.P.166.231; 4.P.166.236; 4.P.166.237; 4.P.166.238; 4.P.166.239; 4.P.166.154; 4.P.166.157; 4.P.166.166; 4.P.166.169; 4.P.166.172; 4.P.166.175; 4.P.166.240; 4.P.166.244; 4.P.169.228; 4.P.169.229; 4.P.169.230; 4.P.169.231; 4.P.169.236; 4.P.169.237; 4.P.169.238; 4.P.169.239; 4.P.169.154; 4.P.169.157; 4.P.169.166; 4.P.169.169; 4.P.169.172; 4.P.169.175; 4.P.169.240; 4.P.169.244; 4.P.172.228; 4.P.172.229; 4.P.172.230; 4.P.172.231; 4.P.172.236; 4.P.172.237; 4.P.172.238; 4.P.172.239; 4.P.172.154; 4.P.172.157; 4.P.172.166; 4.P.172.169; 4.P.172.172; 4.P.172.175; 4.P.172.240; 4.P.172.244; 4.P.175.228; 4.P.175.229; 4.P.175.230; 4.P.175.231; 4.P.175.236; 4.P.175.237; 4.P.175.238; 4.P.175.239; 4.P.175.154; 4.P.175.157; 4.P.175.166; 4.P.175.169; 4.P.175.172; 4.P.175.175; 4.P.175.240; 4.P.175.244; 4.P.240.228; 4.P.240.229; 4.P.240.230; 4.P.240.231; 4.P.240.236; 4.P.240.237; 4.P.240.238; 4.P.240.239; 4.P.240.154; 4.P.240.157; 4.P.240.166; 4.P.240.169; 4.P.240.172; 4.P.240.175; 4.P.240.240; 4.P.240.244; 4.P.244.228; 4.P.244.229; 4.P.244.230; 4.P.244.231; 4.P.244.236; 4.P.244.237; 4.P.244.238; 4.P.244.239; 4.P.244.154; 4.P.244.157; 4.P.244.166; 4.P.244.169; 4.P.244.172; 4.P.244.175; 4.P.244.240; 4.P.244.244;

Prodrugs of 4.U

4.U.228.228; 4.U.228.229; 4.U.228.230; 4.U.228.231; 4.U.228.236; 4.U.228.237; 4.U.228.238; 4.U.228.239; 4.U.228.154; 4.U.228.157; 4.U.228.166; 4.U.228.169; 4.U.228.172; 4.U.228.175; 4.U.228.240; 4.U.228.244; 4.U.229.228; 4.U.229.229; 4.U.229.230; 4.U.229.231; 4.U.229.236; 4.U.229.237; 4.U.229.238; 4.U.229.239; 4.U.229.154; 4.U.229.157; 4.U.229.166; 4.U.229.169; 4.U.229.172; 4.U.229.175; 4.U.229.240; 4.U.229.244; 4.U.230.228; 4.U.230.229; 4.U.230.230; 4.U.230.231; 4.U.230.236; 4.U.230.237; 4.U.230.238; 4.U.230.239; 4.U.230.154; 4.U.230.157; 4.U.230.166; 4.U.230.169; 4.U.230.172; 4.U.230.175; 4.U.230.240; 4.U.230.244; 4.U.231.228; 4.U.231.229; 4.U.231.230; 4.U.231.231; 4.U.231.236; 4.U.231.237; 4.U.231.238; 4.U.231.239; 4.U.231.154; 4.U.231.157; 4.U.231.166; 4.U.231.169; 4.U.231.172; 4.U.231.175; 4.U.231.240; 4.U.231.244; 4.U.236.228; 4.U.236.229; 4.U.236.230; 4.U.236.231; 4.U.236.236; 4.U.236.237; 4.U.236.238; 4.U.236.239; 4.U.236.154; 4.U.236.157; 4.U.236.166; 4.U.236.169; 4.U.236.172; 4.U.236.175; 4.U.236.240; 4.U.236.244; 4.U.237.228; 4.U.237.229; 4.U.237.230; 4.U.237.231; 4.U.237.236; 4.U.237.237; 4.U.237.238; 4.U.237.239; 4.U.237.154; 4.U.237.157; 4.U.237.166; 4.U.237.169; 4.U.237.172; 4.U.237.175; 4.U.237.240; 4.U.237.244; 4.U.238.228; 4.U.238.229; 4.U.238.230; 4.U.238.231; 4.U.238.236; 4.U.238.237; 4.U.238.238; 4.U.238.239; 4.U.238.154; 4.U.238.157; 4.U.238.166; 4.U.238.169; 4.U.238.172; 4.U.238.175; 4.U.238.240; 4.U.238.244; 4.U.239.228; 4.U.239.229; 4.U.239.230; 4.U.239.231; 4.U.239.236; 4.U.239.237; 4.U.239.238; 4.U.239.239; 4.U.239.154; 4.U.239.157; 4.U.239.166; 4.U.239.169; 4.U.239.172; 4.U.239.175; 4.U.239.240; 4.U.239.244; 4.U.154.228; 4.U.154.229; 4.U.154.230; 4.U.154.231; 4.U.154.236; 4.U.154.237; 4.U.154.238; 4.U.154.239; 4.U.154.154; 4.U.154.157; 4.U.154.166; 4.U.154.169; 4.U.154.172; 4.U.154.175; 4.U.154.240; 4.U.154.244; 4.U.157.228;

4.U.157.229; 4.U.157.230; 4.U.157.231; 4.U.157.236; 4.U.157.237; 4.U.157.238; 4.U.157.239; 4.U.157.154; 4.U.157.157; 4.U.157.166; 4.U.157.169; 4.U.157.172; 4.U.157.175; 4.U.157.240; 4.U.157.244; 4.U.166.228; 4.U.166.229; 4.U.166.230; 4.U.166.231; 4.U.166.236; 4.U.166.237; 4.U.166.238; 4.U.166.239; 4.U.166.154; 4.U.166.157; 4.U.166.166; 4.U.166.169; 4.U.166.172; 4.U.166.175; 4.U.166.240; 4.U.166.244; 4.U.169.228; 4.U.169.229; 4.U.169.230; 4.U.169.231; 4.U.169.236; 4.U.169.237; 4.U.169.238; 4.U.169.239; 4.U.169.154; 4.U.169.157; 4.U.169.166; 4.U.169.169; 4.U.169.172; 4.U.169.175; 4.U.169.240; 4.U.169.244; 4.U.172.228; 4.U.172.229; 4.U.172.230; 4.U.172.231; 4.U.172.236; 4.U.172.237; 4.U.172.238; 4.U.172.239; 4.U.172.154; 4.U.172.157; 4.U.172.166; 4.U.172.169; 4.U.172.172; 4.U.172.175; 4.U.172.240; 4.U.172.244; 4.U.175.228; 4.U.175.229; 4.U.175.230; 4.U.175.231; 4.U.175.236; 4.U.175.237; 4.U.175.238; 4.U.175.239; 4.U.175.154; 4.U.175.157; 4.U.175.166; 4.U.175.169; 4.U.175.172; 4.U.175.175; 4.U.175.240; 4.U.175.244; 4.U.240.228; 4.U.240.229; 4.U.240.230; 4.U.240.231; 4.U.240.236; 4.U.240.237; 4.U.240.238; 4.U.240.239; 4.U.240.154; 4.U.240.157; 4.U.240.166; 4.U.240.169; 4.U.240.172; 4.U.240.175; 4.U.240.240; 4.U.240.244; 4.U.244.228; 4.U.244.229; 4.U.244.230; 4.U.244.231; 4.U.244.236; 4.U.244.237; 4.U.244.238; 4.U.244.239; 4.U.244.154; 4.U.244.157; 4.U.244.166; 4.U.244.169; 4.U.244.172; 4.U.244.175; 4.U.244.240; 4.U.244.244;

Prodrugs of 4.W

4.W.228.228; 4.W.228.229; 4.W.228.230; 4.W.228.231; 4.W.228.236; 4.W.228.237; 4.W.228.238; 4.W.228.239; 4.W.228.154; 4.W.228.157; 4.W.228.166; 4.W.228.169; 4.W.228.172; 4.W.228.175; 4.W.228.240; 4.W.228.244; 4.W.229.228; 4.W.229.229; 4.W.229.230; 4.W.229.231; 4.W.229.236; 4.W.229.237; 4.W.229.238; 4.W.229.239; 4.W.229.154;

4.W.229.157; 4.W.229.166; 4.W.229.169; 4.W.229.172; 4.W.229.175; 4.W.229.240; 4.W.229.244; 4.W.230.228; 4.W.230.229; 4.W.230.230; 4.W.230.231; 4.W.230.236; 4.W.230.237; 4.W.230.238; 4.W.230.239; 4.W.230.154; 4.W.230.157; 4.W.230.166; 4.W.230.169; 4.W.230.172; 4.W.230.175; 4.W.230.240; 4.W.230.244; 4.W.231.228; 4.W.231.229; 4.W.231.230; 4.W.231.231; 4.W.231.236; 4.W.231.237; 4.W.231.238; 4.W.231.239; 4.W.231.154; 4.W.231.157; 4.W.231.166; 4.W.231.169; 4.W.231.172; 4.W.231.175; 4.W.231.240; 4.W.231.244; 4.W.236.228; 4.W.236.229; 4.W.236.230; 4.W.236.231; 4.W.236.236; 4.W.236.237; 4.W.236.238; 4.W.236.239; 4.W.236.154; 4.W.236.157; 4.W.236.166; 4.W.236.169; 4.W.236.172; 4.W.236.175; 4.W.236.240; 4.W.236.244; 4.W.237.228; 4.W.237.229; 4.W.237.230; 4.W.237.231; 4.W.237.236; 4.W.237.237; 4.W.237.238; 4.W.237.239; 4.W.237.154; 4.W.237.157; 4.W.237.166; 4.W.237.169; 4.W.237.172; 4.W.237.175; 4.W.237.240; 4.W.237.244; 4.W.238.228; 4.W.238.229; 4.W.238.230; 4.W.238.231; 4.W.238.236; 4.W.238.237; 4.W.238.238; 4.W.238.239; 4.W.238.154; 4.W.238.157; 4.W.238.166; 4.W.238.169; 4.W.238.172; 4.W.238.175; 4.W.238.240; 4.W.238.244; 4.W.239.228; 4.W.239.229; 4.W.239.230; 4.W.239.231; 4.W.239.236; 4.W.239.237; 4.W.239.238; 4.W.239.239; 4.W.239.154; 4.W.239.157; 4.W.239.166; 4.W.239.169; 4.W.239.172; 4.W.239.175; 4.W.239.240; 4.W.239.244; 4.W.154.228; 4.W.154.229; 4.W.154.230; 4.W.154.231; 4.W.154.236; 4.W.154.237; 4.W.154.238; 4.W.154.239; 4.W.154.154; 4.W.154.157; 4.W.154.166; 4.W.154.169; 4.W.154.172; 4.W.154.175; 4.W.154.240; 4.W.154.244; 4.W.157.228; 4.W.157.229; 4.W.157.230; 4.W.157.231; 4.W.157.236; 4.W.157.237; 4.W.157.238; 4.W.157.239; 4.W.157.154; 4.W.157.157; 4.W.157.166; 4.W.157.169; 4.W.157.172; 4.W.157.175; 4.W.157.240; 4.W.157.244; 4.W.166.228; 4.W.166.229; 4.W.166.230; 4.W.166.231; 4.W.166.236; 4.W.166.237; 4.W.166.238; 4.W.166.239; 4.W.166.154; 4.W.166.157; 4.W.166.166; 4.W.166.169; 4.W.166.172; 4.W.166.175; 4.W.166.240;

4.W.166.244; 4.W.169.228; 4.W.169.229; 4.W.169.230; 4.W.169.231; 4.W.169.236; 4.W.169.237; 4.W.169.238; 4.W.169.239; 4.W.169.154; 4.W.169.157; 4.W.169.166; 4.W.169.169; 4.W.169.172; 4.W.169.175; 4.W.169.240; 4.W.169.244; 4.W.172.228; 4.W.172.229; 4.W.172.230; 4.W.172.231; 4.W.172.236; 4.W.172.237; 4.W.172.238; 4.W.172.239; 4.W.172.154; 4.W.172.157; 4.W.172.166; 4.W.172.169; 4.W.172.172; 4.W.172.175; 4.W.172.240; 4.W.172.244; 4.W.175.228; 4.W.175.229; 4.W.175.230; 4.W.175.231; 4.W.175.236; 4.W.175.237; 4.W.175.238; 4.W.175.239; 4.W.175.154; 4.W.175.157; 4.W.175.166; 4.W.175.169; 4.W.175.172; 4.W.175.175; 4.W.175.240; 4.W.175.244; 4.W.240.228; 4.W.240.229; 4.W.240.230; 4.W.240.231; 4.W.240.236; 4.W.240.237; 4.W.240.238; 4.W.240.239; 4.W.240.154; 4.W.240.157; 4.W.240.166; 4.W.240.169; 4.W.240.172; 4.W.240.175; 4.W.240.240; 4.W.240.244; 4.W.244.228; 4.W.244.229; 4.W.244.230; 4.W.244.231; 4.W.244.236; 4.W.244.237; 4.W.244.238; 4.W.244.239; 4.W.244.154; 4.W.244.157; 4.W.244.166; 4.W.244.169; 4.W.244.172; 4.W.244.175; 4.W.244.240; 4.W.244.244;

Prodrugs of 4.Y

4.Y.228.228; 4.Y.228.229; 4.Y.228.230; 4.Y.228.231; 4.Y.228.236; 4.Y.228.237; 4.Y.228.238; 4.Y.228.239; 4.Y.228.154; 4.Y.228.157; 4.Y.228.166; 4.Y.228.169; 4.Y.228.172; 4.Y.228.175; 4.Y.228.240; 4.Y.228.244; 4.Y.229.228; 4.Y.229.229; 4.Y.229.230; 4.Y.229.231; 4.Y.229.236; 4.Y.229.237; 4.Y.229.238; 4.Y.229.239; 4.Y.229.154; 4.Y.229.157; 4.Y.229.166; 4.Y.229.169; 4.Y.229.172; 4.Y.229.175; 4.Y.229.240; 4.Y.229.244; 4.Y.230.228; 4.Y.230.229; 4.Y.230.230; 4.Y.230.231; 4.Y.230.236; 4.Y.230.237; 4.Y.230.238; 4.Y.230.239; 4.Y.230.154; 4.Y.230.157; 4.Y.230.166; 4.Y.230.169; 4.Y.230.172; 4.Y.230.175; 4.Y.230.240; 4.Y.230.244; 4.Y.231.228; 4.Y.231.229; 4.Y.231.230; 4.Y.231.231; 4.Y.231.236; 4.Y.231.237; 4.Y.231.238; 4.Y.231.239; 4.Y.231.154; 4.Y.231.157; 4.Y.231.166; 4.Y.231.169; 4.Y.231.172; 4.Y.231.175; 4.Y.231.240; 4.Y.231.244; 4.Y.236.228;

4.Y.236.229; 4.Y.236.230; 4.Y.236.231; 4.Y.236.236; 4.Y.236.237; 4.Y.236.238; 4.Y.236.239; 4.Y.236.154; 4.Y.236.157; 4.Y.236.166; 4.Y.236.169; 4.Y.236.172; 4.Y.236.175; 4.Y.236.240; 4.Y.236.244; 4.Y.237.228; 4.Y.237.229; 4.Y.237.230; 4.Y.237.231; 4.Y.237.236; 4.Y.237.237; 4.Y.237.238; 4.Y.237.239; 4.Y.237.154; 4.Y.237.157; 4.Y.237.166; 4.Y.237.169; 4.Y.237.172; 4.Y.237.175; 4.Y.237.240; 4.Y.237.244; 4.Y.238.228; 4.Y.238.229; 4.Y.238.230; 4.Y.238.231; 4.Y.238.236; 4.Y.238.237; 4.Y.238.238; 4.Y.238.239; 4.Y.238.154; 4.Y.238.157; 4.Y.238.166; 4.Y.238.169; 4.Y.238.172; 4.Y.238.175; 4.Y.238.240; 4.Y.238.244; 4.Y.239.228; 4.Y.239.229; 4.Y.239.230; 4.Y.239.231; 4.Y.239.236; 4.Y.239.237; 4.Y.239.238; 4.Y.239.239; 4.Y.239.154; 4.Y.239.157; 4.Y.239.166; 4.Y.239.169; 4.Y.239.172; 4.Y.239.175; 4.Y.239.240; 4.Y.239.244; 4.Y.154.228; 4.Y.154.229; 4.Y.154.230; 4.Y.154.231; 4.Y.154.236; 4.Y.154.237; 4.Y.154.238; 4.Y.154.239; 4.Y.154.154; 4.Y.154.157; 4.Y.154.166; 4.Y.154.169; 4.Y.154.172; 4.Y.154.175; 4.Y.154.240; 4.Y.154.244; 4.Y.157.228; 4.Y.157.229; 4.Y.157.230; 4.Y.157.231; 4.Y.157.236; 4.Y.157.237; 4.Y.157.238; 4.Y.157.239; 4.Y.157.154; 4.Y.157.157; 4.Y.157.166; 4.Y.157.169; 4.Y.157.172; 4.Y.157.175; 4.Y.157.240; 4.Y.157.244; 4.Y.166.228; 4.Y.166.229; 4.Y.166.230; 4.Y.166.231; 4.Y.166.236; 4.Y.166.237; 4.Y.166.238; 4.Y.166.239; 4.Y.166.154; 4.Y.166.157; 4.Y.166.166; 4.Y.166.169; 4.Y.166.172; 4.Y.166.175; 4.Y.166.240; 4.Y.166.244; 4.Y.169.228; 4.Y.169.229; 4.Y.169.230; 4.Y.169.231; 4.Y.169.236; 4.Y.169.237; 4.Y.169.238; 4.Y.169.239; 4.Y.169.154; 4.Y.169.157; 4.Y.169.166; 4.Y.169.169; 4.Y.169.172; 4.Y.169.175; 4.Y.169.240; 4.Y.169.244; 4.Y.172.228; 4.Y.172.229; 4.Y.172.230; 4.Y.172.231; 4.Y.172.236; 4.Y.172.237; 4.Y.172.238; 4.Y.172.239; 4.Y.172.154; 4.Y.172.157; 4.Y.172.166; 4.Y.172.169; 4.Y.172.172; 4.Y.172.175; 4.Y.172.240; 4.Y.172.244; 4.Y.175.228; 4.Y.175.229; 4.Y.175.230; 4.Y.175.231; 4.Y.175.236; 4.Y.175.237; 4.Y.175.238; 4.Y.175.239; 4.Y.175.154; 4.Y.175.157; 4.Y.175.166; 4.Y.175.169; 4.Y.175.172; 4.Y.175.175; 4.Y.175.240; 4.Y.175.244; 4.Y.240.228; 4.Y.240.229; 4.Y.240.230; 4.Y.240.231; 4.Y.240.236; 4.Y.240.237; 4.Y.240.238; 4.Y.240.239; 4.Y.240.154; 4.Y.240.157; 4.Y.240.166; 4.Y.240.169; 4.Y.240.172; 4.Y.240.175; 4.Y.240.240; 4.Y.240.244; 4.Y.244.228; 4.Y.244.229; 4.Y.244.230; 4.Y.244.231; 4.Y.244.236;

4.Y.244.237; 4.Y.244.238; 4.Y.244.239; 4.Y.244.154; 4.Y.244.157; 4.Y.244.166; 4.Y.244.169; 4.Y.244.172; 4.Y.244.175; 4.Y.244.240; 4.Y.244.244;

Prodrugs of 5.B

5.B.228.228; 5.B.228.229; 5.B.228.230; 5.B.228.231; 5.B.228.236; 5.B.228.237; 5.B.228.238; 5.B.228.239; 5.B.228.154; 5.B.228.157; 5.B.228.166; 5.B.228.169; 5.B.228.172; 5.B.228.175; 5.B.228.240; 5.B.228.244; 5.B.229.228; 5.B.229.229; 5.B.229.230; 5.B.229.231; 5.B.229.236; 5.B.229.237; 5.B.229.238; 5.B.229.239; 5.B.229.154; 5.B.229.157; 5.B.229.166; 5.B.229.169; 5.B.229.172; 5.B.229.175; 5.B.229.240; 5.B.229.244; 5.B.230.228; 5.B.230.229; 5.B.230.230; 5.B.230.231; 5.B.230.236; 5.B.230.237; 5.B.230.238; 5.B.230.239; 5.B.230.154; 5.B.230.157; 5.B.230.166; 5.B.230.169; 5.B.230.172; 5.B.230.175; 5.B.230.240; 5.B.230.244; 5.B.231.228; 5.B.231.229; 5.B.231.230; 5.B.231.231; 5.B.231.236; 5.B.231.237; 5.B.231.238; 5.B.231.239; 5.B.231.154; 5.B.231.157; 5.B.231.166; 5.B.231.169; 5.B.231.172; 5.B.231.175; 5.B.231.240; 5.B.231.244; 5.B.236.228; 5.B.236.229; 5.B.236.230; 5.B.236.231; 5.B.236.236; 5.B.236.237; 5.B.236.238; 5.B.236.239; 5.B.236.154; 5.B.236.157; 5.B.236.166; 5.B.236.169; 5.B.236.172; 5.B.236.175; 5.B.236.240; 5.B.236.244; 5.B.237.228; 5.B.237.229; 5.B.237.230; 5.B.237.231; 5.B.237.236; 5.B.237.237; 5.B.237.238; 5.B.237.239; 5.B.237.154; 5.B.237.157; 5.B.237.166; 5.B.237.169; 5.B.237.172; 5.B.237.175; 5.B.237.240; 5.B.237.244; 5.B.238.228; 5.B.238.229; 5.B.238.230; 5.B.238.231; 5.B.238.236; 5.B.238.237; 5.B.238.238; 5.B.238.239; 5.B.238.154; 5.B.238.157; 5.B.238.166; 5.B.238.169; 5.B.238.172; 5.B.238.175; 5.B.238.240; 5.B.238.244; 5.B.239.228; 5.B.239.229; 5.B.239.230; 5.B.239.231; 5.B.239.236; 5.B.239.237; 5.B.239.238; 5.B.239.239; 5.B.239.154; 5.B.239.157; 5.B.239.166; 5.B.239.169; 5.B.239.172; 5.B.239.175; 5.B.239.240; 5.B.239.244; 5.B.154.228; 5.B.154.229; 5.B.154.230; 5.B.154.231; 5.B.154.236; 5.B.154.237; 5.B.154.238; 5.B.154.239; 5.B.154.154; 5.B.154.157; 5.B.154.166; 5.B.154.169; 5.B.154.172; 5.B.154.175; 5.B.154.240; 5.B.154.244; 5.B.157.228; 5.B.157.229; 5.B.157.230; 5.B.157.231; 5.B.157.236; 5.B.157.237; 5.B.157.238; 5.B.157.239; 5.B.157.154; 5.B.157.157; 5.B.157.166;

5.B.157.169; 5.B.157.172; 5.B.157.175; 5.B.157.240; 5.B.157.244; 5.B.166.228; 5.B.166.229; 5.B.166.230; 5.B.166.231; 5.B.166.236; 5.B.166.237; 5.B.166.238; 5.B.166.239; 5.B.166.154; 5.B.166.157; 5.B.166.166; 5.B.166.169; 5.B.166.172; 5.B.166.175; 5.B.166.240; 5.B.166.244; 5.B.169.228; 5.B.169.229; 5.B.169.230; 5.B.169.231; 5.B.169.236; 5.B.169.237; 5.B.169.238; 5.B.169.239; 5.B.169.154; 5.B.169.157; 5.B.169.166; 5.B.169.169; 5.B.169.172; 5.B.169.175; 5.B.169.240; 5.B.169.244; 5.B.172.228; 5.B.172.229; 5.B.172.230; 5.B.172.231; 5.B.172.236; 5.B.172.237; 5.B.172.238; 5.B.172.239; 5.B.172.154; 5.B.172.157; 5.B.172.166; 5.B.172.169; 5.B.172.172; 5.B.172.175; 5.B.172.240; 5.B.172.244; 5.B.175.228; 5.B.175.229; 5.B.175.230; 5.B.175.231; 5.B.175.236; 5.B.175.237; 5.B.175.238; 5.B.175.239; 5.B.175.154; 5.B.175.157; 5.B.175.166; 5.B.175.169; 5.B.175.172; 5.B.175.175; 5.B.175.240; 5.B.175.244; 5.B.240.228; 5.B.240.229; 5.B.240.230; 5.B.240.231; 5.B.240.236; 5.B.240.237; 5.B.240.238; 5.B.240.239; 5.B.240.154; 5.B.240.157; 5.B.240.166; 5.B.240.169; 5.B.240.172; 5.B.240.175; 5.B.240.240; 5.B.240.244; 5.B.244.228; 5.B.244.229; 5.B.244.230; 5.B.244.231; 5.B.244.236; 5.B.244.237; 5.B.244.238; 5.B.244.239; 5.B.244.154; 5.B.244.157; 5.B.244.166; 5.B.244.169; 5.B.244.172; 5.B.244.175; 5.B.244.240; 5.B.244.244;

Prodrugs of 5.D

5.D.228.228; 5.D.228.229; 5.D.228.230; 5.D.228.231; 5.D.228.236; 5.D.228.237; 5.D.228.238; 5.D.228.239; 5.D.228.154; 5.D.228.157; 5.D.228.166; 5.D.228.169; 5.D.228.172; 5.D.228.175; 5.D.228.240; 5.D.228.244; 5.D.229.228; 5.D.229.229; 5.D.229.230; 5.D.229.231; 5.D.229.236; 5.D.229.237; 5.D.229.238; 5.D.229.239; 5.D.229.154; 5.D.229.157; 5.D.229.166; 5.D.229.169; 5.D.229.172; 5.D.229.175; 5.D.229.240; 5.D.229.244; 5.D.230.228; 5.D.230.229; 5.D.230.230; 5.D.230.231; 5.D.230.236; 5.D.230.237; 5.D.230.238; 5.D.230.239; 5.D.230.154; 5.D.230.157; 5.D.230.166; 5.D.230.169; 5.D.230.172; 5.D.230.175; 5.D.230.240; 5.D.230.244; 5.D.231.228; 5.D.231.229; 5.D.231.230; 5.D.231.231; 5.D.231.236; 5.D.231.237; 5.D.231.238;

5.D.231.239; 5.D.231.154; 5.D.231.157; 5.D.231.166; 5.D.231.169; 5.D.231.172; 5.D.231.175; 5.D.231.240; 5.D.231.244; 5.D.236.228; 5.D.236.229; 5.D.236.230; 5.D.236.231; 5.D.236.236; 5.D.236.237; 5.D.236.238; 5.D.236.239; 5.D.236.154; 5.D.236.157; 5.D.236.166; 5.D.236.169; 5.D.236.172; 5.D.236.175; 5.D.236.240; 5.D.236.244; 5.D.237.228; 5.D.237.229; 5.D.237.230; 5.D.237.231; 5.D.237.236; 5.D.237.237; 5.D.237.238; 5.D.237.239; 5.D.237.154; 5.D.237.157; 5.D.237.166; 5.D.237.169; 5.D.237.172; 5.D.237.175; 5.D.237.240; 5.D.237.244; 5.D.238.228; 5.D.238.229; 5.D.238.230; 5.D.238.231; 5.D.238.236; 5.D.238.237; 5.D.238.238; 5.D.238.239; 5.D.238.154; 5.D.238.157; 5.D.238.166; 5.D.238.169; 5.D.238.172; 5.D.238.175; 5.D.238.240; 5.D.238.244; 5.D.239.228; 5.D.239.229; 5.D.239.230; 5.D.239.231; 5.D.239.236; 5.D.239.237; 5.D.239.238; 5.D.239.239; 5.D.239.154; 5.D.239.157; 5.D.239.166; 5.D.239.169; 5.D.239.172; 5.D.239.175; 5.D.239.240; 5.D.239.244; 5.D.154.228; 5.D.154.229; 5.D.154.230; 5.D.154.231; 5.D.154.236; 5.D.154.237; 5.D.154.238; 5.D.154.239; 5.D.154.154; 5.D.154.157; 5.D.154.166; 5.D.154.169; 5.D.154.172; 5.D.154.175; 5.D.154.240; 5.D.154.244; 5.D.157.228; 5.D.157.229; 5.D.157.230; 5.D.157.231; 5.D.157.236; 5.D.157.237; 5.D.157.238; 5.D.157.239; 5.D.157.154; 5.D.157.157; 5.D.157.166; 5.D.157.169; 5.D.157.172; 5.D.157.175; 5.D.157.240; 5.D.157.244; 5.D.166.228; 5.D.166.229; 5.D.166.230; 5.D.166.231; 5.D.166.236; 5.D.166.237; 5.D.166.238; 5.D.166.239; 5.D.166.154; 5.D.166.157; 5.D.166.166; 5.D.166.169; 5.D.166.172; 5.D.166.175; 5.D.166.240; 5.D.166.244; 5.D.169.228; 5.D.169.229; 5.D.169.230; 5.D.169.231; 5.D.169.236; 5.D.169.237; 5.D.169.238; 5.D.169.239; 5.D.169.154; 5.D.169.157; 5.D.169.166; 5.D.169.169; 5.D.169.172; 5.D.169.175; 5.D.169.240; 5.D.169.244; 5.D.172.228; 5.D.172.229; 5.D.172.230; 5.D.172.231; 5.D.172.236; 5.D.172.237; 5.D.172.238; 5.D.172.239; 5.D.172.154; 5.D.172.157; 5.D.172.166; 5.D.172.169; 5.D.172.172;

5.D.172.175; 5.D.172.240; 5.D.172.244; 5.D.175.228; 5.D.175.229; 5.D.175.230; 5.D.175.231; 5.D.175.236; 5.D.175.237; 5.D.175.238; 5.D.175.239; 5.D.175.154; 5.D.175.157; 5.D.175.166; 5.D.175.169; 5.D.175.172; 5.D.175.175; 5.D.175.240; 5.D.175.244; 5.D.240.228; 5.D.240.229; 5.D.240.230; 5.D.240.231; 5.D.240.236; 5.D.240.237; 5.D.240.238; 5.D.240.239; 5.D.240.154; 5.D.240.157; 5.D.240.166; 5.D.240.169; 5.D.240.172; 5.D.240.175; 5.D.240.240; 5.D.240.244; 5.D.244.228; 5.D.244.229; 5.D.244.230; 5.D.244.231; 5.D.244.236; 5.D.244.237; 5.D.244.238; 5.D.244.239; 5.D.244.154; 5.D.244.157; 5.D.244.166; 5.D.244.169; 5.D.244.172; 5.D.244.175; 5.D.244.240; 5.D.244.244;

Prodrugs of 5.E

5.E.228.228; 5.E.228.229; 5.E.228.230; 5.E.228.231; 5.E.228.236; 5.E.228.237; 5.E.228.238; 5.E.228.239; 5.E.228.154; 5.E.228.157; 5.E.228.166; 5.E.228.169; 5.E.228.172; 5.E.228.175; 5.E.228.240; 5.E.228.244; 5.E.229.228; 5.E.229.229; 5.E.229.230; 5.E.229.231; 5.E.229.236; 5.E.229.237; 5.E.229.238; 5.E.229.239; 5.E.229.154; 5.E.229.157; 5.E.229.166; 5.E.229.169; 5.E.229.172; 5.E.229.175; 5.E.229.240; 5.E.229.244; 5.E.230.228; 5.E.230.229; 5.E.230.230; 5.E.230.231; 5.E.230.236; 5.E.230.237; 5.E.230.238; 5.E.230.239; 5.E.230.154; 5.E.230.157; 5.E.230.166; 5.E.230.169; 5.E.230.172; 5.E.230.175; 5.E.230.240; 5.E.230.244; 5.E.231.228; 5.E.231.229; 5.E.231.230; 5.E.231.231; 5.E.231.236; 5.E.231.237; 5.E.231.238; 5.E.231.239; 5.E.231.154; 5.E.231.157; 5.E.231.166; 5.E.231.169; 5.E.231.172; 5.E.231.175; 5.E.231.240; 5.E.231.244; 5.E.236.228; 5.E.236.229; 5.E.236.230; 5.E.236.231; 5.E.236.236; 5.E.236.237; 5.E.236.238; 5.E.236.239; 5.E.236.154; 5.E.236.157; 5.E.236.166; 5.E.236.169; 5.E.236.172; 5.E.236.175; 5.E.236.240; 5.E.236.244; 5.E.237.228; 5.E.237.229; 5.E.237.230; 5.E.237.231; 5.E.237.236; 5.E.237.237; 5.E.237.238; 5.E.237.239; 5.E.237.154; 5.E.237.157; 5.E.237.166; 5.E.237.169; 5.E.237.172; 5.E.237.175; 5.E.237.240; 5.E.237.244; 5.E.238.228; 5.E.238.229; 5.E.238.230; 5.E.238.231; 5.E.238.236;

5.E.238.237; 5.E.238.238; 5.E.238.239; 5.E.238.154; 5.E.238.157; 5.E.238.166; 5.E.238.169; 5.E.238.172; 5.E.238.175; 5.E.238.240; 5.E.238.244; 5.E.239.228; 5.E.239.229; 5.E.239.230; 5.E.239.231; 5.E.239.236; 5.E.239.237; 5.E.239.238; 5.E.239.239; 5.E.239.154; 5.E.239.157; 5.E.239.166; 5.E.239.169; 5.E.239.172; 5.E.239.175; 5.E.239.240; 5.E.239.244; 5.E.154.228; 5.E.154.229; 5.E.154.230; 5.E.154.231; 5.E.154.236; 5.E.154.237; 5.E.154.238; 5.E.154.239; 5.E.154.154; 5.E.154.157; 5.E.154.166; 5.E.154.169; 5.E.154.172; 5.E.154.175; 5.E.154.240; 5.E.154.244; 5.E.157.228; 5.E.157.229; 5.E.157.230; 5.E.157.231; 5.E.157.236; 5.E.157.237; 5.E.157.238; 5.E.157.239; 5.E.157.154; 5.E.157.157; 5.E.157.166; 5.E.157.169; 5.E.157.172; 5.E.157.175; 5.E.157.240; 5.E.157.244; 5.E.166.228; 5.E.166.229; 5.E.166.230; 5.E.166.231; 5.E.166.236; 5.E.166.237; 5.E.166.238; 5.E.166.239; 5.E.166.154; 5.E.166.157; 5.E.166.166; 5.E.166.169; 5.E.166.172; 5.E.166.175; 5.E.166.240; 5.E.166.244; 5.E.169.228; 5.E.169.229; 5.E.169.230; 5.E.169.231; 5.E.169.236; 5.E.169.237; 5.E.169.238; 5.E.169.239; 5.E.169.154; 5.E.169.157; 5.E.169.166; 5.E.169.169; 5.E.169.172; 5.E.169.175; 5.E.169.240; 5.E.169.244; 5.E.172.228; 5.E.172.229; 5.E.172.230; 5.E.172.231; 5.E.172.236; 5.E.172.237; 5.E.172.238; 5.E.172.239; 5.E.172.154; 5.E.172.157; 5.E.172.166; 5.E.172.169; 5.E.172.172; 5.E.172.175; 5.E.172.240; 5.E.172.244; 5.E.175.228; 5.E.175.229; 5.E.175.230; 5.E.175.231; 5.E.175.236; 5.E.175.237; 5.E.175.238; 5.E.175.239; 5.E.175.154; 5.E.175.157; 5.E.175.166; 5.E.175.169; 5.E.175.172; 5.E.175.175; 5.E.175.240; 5.E.175.244; 5.E.240.228; 5.E.240.229; 5.E.240.230; 5.E.240.231; 5.E.240.236; 5.E.240.237; 5.E.240.238; 5.E.240.239; 5.E.240.154; 5.E.240.157; 5.E.240.166; 5.E.240.169; 5.E.240.172; 5.E.240.175; 5.E.240.240; 5.E.240.244; 5.E.244.228; 5.E.244.229; 5.E.244.230; 5.E.244.231; 5.E.244.236; 5.E.244.237; 5.E.244.238; 5.E.244.239; 5.E.244.154; 5.E.244.157; 5.E.244.166; 5.E.244.169; 5.E.244.172; 5.E.244.175; 5.E.244.240; 5.E.244.244;

Prodrugs of 5.G

5.G.228.228; 5.G.228.229; 5.G.228.230; 5.G.228.231; 5.G.228.236; 5.G.228.237; 5.G.228.238; 5.G.228.239; 5.G.228.154; 5.G.228.157;

5.G.228.166; 5.G.228.169; 5.G.228.172; 5.G.228.175; 5.G.228.240; 5.G.228.244; 5.G.229.228; 5.G.229.229; 5.G.229.230; 5.G.229.231; 5.G.229.236; 5.G.229.237; 5.G.229.238; 5.G.229.239; 5.G.229.154; 5.G.229.157; 5.G.229.166; 5.G.229.169; 5.G.229.172; 5.G.229.175; 5.G.229.240; 5.G.229.244; 5.G.230.228; 5.G.230.229; 5.G.230.230; 5.G.230.231; 5.G.230.236; 5.G.230.237; 5.G.230.238; 5.G.230.239; 5.G.230.154; 5.G.230.157; 5.G.230.166; 5.G.230.169; 5.G.230.172; 5.G.230.175; 5.G.230.240; 5.G.230.244; 5.G.231.228; 5.G.231.229; 5.G.231.230; 5.G.231.231; 5.G.231.236; 5.G.231.237; 5.G.231.238; 5.G.231.239; 5.G.231.154; 5.G.231.157; 5.G.231.166; 5.G.231.169; 5.G.231.172; 5.G.231.175; 5.G.231.240; 5.G.231.244; 5.G.236.228; 5.G.236.229; 5.G.236.230; 5.G.236.231; 5.G.236.236; 5.G.236.237; 5.G.236.238; 5.G.236.239; 5.G.236.154; 5.G.236.157; 5.G.236.166; 5.G.236.169; 5.G.236.172; 5.G.236.175; 5.G.236.240; 5.G.236.244; 5.G.237.228; 5.G.237.229; 5.G.237.230; 5.G.237.231; 5.G.237.236; 5.G.237.237; 5.G.237.238; 5.G.237.239; 5.G.237.154; 5.G.237.157; 5.G.237.166; 5.G.237.169; 5.G.237.172; 5.G.237.175; 5.G.237.240; 5.G.237.244; 5.G.238.228; 5.G.238.229; 5.G.238.230; 5.G.238.231; 5.G.238.236; 5.G.238.237; 5.G.238.238; 5.G.238.239; 5.G.238.154; 5.G.238.157; 5.G.238.166; 5.G.238.169; 5.G.238.172; 5.G.238.175; 5.G.238.240; 5.G.238.244; 5.G.239.228; 5.G.239.229; 5.G.239.230; 5.G.239.231; 5.G.239.236; 5.G.239.237; 5.G.239.238; 5.G.239.239; 5.G.239.154; 5.G.239.157; 5.G.239.166; 5.G.239.169; 5.G.239.172; 5.G.239.175; 5.G.239.240; 5.G.239.244; 5.G.154.228; 5.G.154.229; 5.G.154.230; 5.G.154.231; 5.G.154.236; 5.G.154.237; 5.G.154.238; 5.G.154.239; 5.G.154.154; 5.G.154.157; 5.G.154.166; 5.G.154.169; 5.G.154.172; 5.G.154.175; 5.G.154.240; 5.G.154.244; 5.G.157.228; 5.G.157.229; 5.G.157.230; 5.G.157.231; 5.G.157.236; 5.G.157.237; 5.G.157.238; 5.G.157.239; 5.G.157.154; 5.G.157.157; 5.G.157.166; 5.G.157.169; 5.G.157.172; 5.G.157.175; 5.G.157.240; 5.G.157.244;

5.G.166.228; 5.G.166.229; 5.G.166.230; 5.G.166.231; 5.G.166.236; 5.G.166.237; 5.G.166.238; 5.G.166.239; 5.G.166.154; 5.G.166.157; 5.G.166.166; 5.G.166.169; 5.G.166.172; 5.G.166.175; 5.G.166.240; 5.G.166.244; 5.G.169.228; 5.G.169.229; 5.G.169.230; 5.G.169.231; 5.G.169.236; 5.G.169.237; 5.G.169.238; 5.G.169.239; 5.G.169.154; 5.G.169.157; 5.G.169.166; 5.G.169.169; 5.G.169.172; 5.G.169.175; 5.G.169.240; 5.G.169.244; 5.G.172.228; 5.G.172.229; 5.G.172.230; 5.G.172.231; 5.G.172.236; 5.G.172.237; 5.G.172.238; 5.G.172.239; 5.G.172.154; 5.G.172.157; 5.G.172.166; 5.G.172.169; 5.G.172.172; 5.G.172.175; 5.G.172.240; 5.G.172.244; 5.G.175.228; 5.G.175.229; 5.G.175.230; 5.G.175.231; 5.G.175.236; 5.G.175.237; 5.G.175.238; 5.G.175.239; 5.G.175.154; 5.G.175.157; 5.G.175.166; 5.G.175.169; 5.G.175.172; 5.G.175.175; 5.G.175.240; 5.G.175.244; 5.G.240.228; 5.G.240.229; 5.G.240.230; 5.G.240.231; 5.G.240.236; 5.G.240.237; 5.G.240.238; 5.G.240.239; 5.G.240.154; 5.G.240.157; 5.G.240.166; 5.G.240.169; 5.G.240.172; 5.G.240.175; 5.G.240.240; 5.G.240.244; 5.G.244.228; 5.G.244.229; 5.G.244.230; 5.G.244.231; 5.G.244.236; 5.G.244.237; 5.G.244.238; 5.G.244.239; 5.G.244.154; 5.G.244.157; 5.G.244.166; 5.G.244.169; 5.G.244.172; 5.G.244.175; 5.G.244.240; 5.G.244.244;

Prodrugs of 5.I

5.I.228.228; 5.I.228.229; 5.I.228.230; 5.I.228.231; 5.I.228.236; 5.I.228.237; 5.I.228.238; 5.I.228.239; 5.I.228.154; 5.I.228.157; 5.I.228.166; 5.I.228.169; 5.I.228.172; 5.I.228.175; 5.I.228.240; 5.I.228.244; 5.I.229.228; 5.I.229.229; 5.I.229.230; 5.I.229.231; 5.I.229.236; 5.I.229.237; 5.I.229.238; 5.I.229.239; 5.I.229.154; 5.I.229.157; 5.I.229.166; 5.I.229.169; 5.I.229.172; 5.I.229.175; 5.I.229.240; 5.I.229.244; 5.I.230.228; 5.I.230.229; 5.I.230.230; 5.I.230.231; 5.I.230.236; 5.I.230.237; 5.I.230.238; 5.I.230.239; 5.I.230.154; 5.I.230.157; 5.I.230.166; 5.I.230.169; 5.I.230.172; 5.I.230.175; 5.I.230.240; 5.I.230.244;

5.I.231.228; 5.I.231.229; 5.I.231.230; 5.I.231.231; 5.I.231.236; 5.I.231.237; 5.I.231.238; 5.I.231.239; 5.I.231.154; 5.I.231.157; 5.I.231.166; 5.I.231.169; 5.I.231.172; 5.I.231.175; 5.I.231.240; 5.I.231.244; 5.I.236.228; 5.I.236.229; 5.I.236.230; 5.I.236.231; 5.I.236.236; 5.I.236.237; 5.I.236.238; 5.I.236.239; 5.I.236.154; 5.I.236.157; 5.I.236.166; 5.I.236.169; 5.I.236.172; 5.I.236.175; 5.I.236.240; 5.I.236.244; 5.I.237.228; 5.I.237.229; 5.I.237.230; 5.I.237.231; 5.I.237.236; 5.I.237.237; 5.I.237.238; 5.I.237.239; 5.I.237.154; 5.I.237.157; 5.I.237.166; 5.I.237.169; 5.I.237.172; 5.I.237.175; 5.I.237.240; 5.I.237.244; 5.I.238.228; 5.I.238.229; 5.I.238.230; 5.I.238.231; 5.I.238.236; 5.I.238.237; 5.I.238.238; 5.I.238.239; 5.I.238.154; 5.I.238.157; 5.I.238.166; 5.I.238.169; 5.I.238.172; 5.I.238.175; 5.I.238.240; 5.I.238.244; 5.I.239.228; 5.I.239.229; 5.I.239.230; 5.I.239.231; 5.I.239.236; 5.I.239.237; 5.I.239.238; 5.I.239.239; 5.I.239.154; 5.I.239.157; 5.I.239.166; 5.I.239.169; 5.I.239.172; 5.I.239.175; 5.I.239.240; 5.I.239.244; 5.I.154.228; 5.I.154.229; 5.I.154.230; 5.I.154.231; 5.I.154.236; 5.I.154.237; 5.I.154.238; 5.I.154.239; 5.I.154.154; 5.I.154.157; 5.I.154.166; 5.I.154.169; 5.I.154.172; 5.I.154.175; 5.I.154.240; 5.I.154.244; 5.I.157.228; 5.I.157.229; 5.I.157.230; 5.I.157.231; 5.I.157.236; 5.I.157.237; 5.I.157.238; 5.I.157.239; 5.I.157.154; 5.I.157.157; 5.I.157.166; 5.I.157.169; 5.I.157.172; 5.I.157.175; 5.I.157.240; 5.I.157.244; 5.I.166.228; 5.I.166.229; 5.I.166.230; 5.I.166.231; 5.I.166.236; 5.I.166.237; 5.I.166.238; 5.I.166.239; 5.I.166.154; 5.I.166.157; 5.I.166.166; 5.I.166.169; 5.I.166.172; 5.I.166.175; 5.I.166.240; 5.I.166.244; 5.I.169.228; 5.I.169.229; 5.I.169.230; 5.I.169.231; 5.I.169.236; 5.I.169.237; 5.I.169.238; 5.I.169.239; 5.I.169.154; 5.I.169.157; 5.I.169.166; 5.I.169.169; 5.I.169.172; 5.I.169.175; 5.I.169.240; 5.I.169.244; 5.I.172.228; 5.I.172.229; 5.I.172.230; 5.I.172.231; 5.I.172.236; 5.I.172.237; 5.I.172.238; 5.I.172.239; 5.I.172.154; 5.I.172.157; 5.I.172.166; 5.I.172.169; 5.I.172.172; 5.I.172.175; 5.I.172.240; 5.I.172.244; 5.I.175.228; 5.I.175.229; 5.I.175.230; 5.I.175.231; 5.I.175.236; 5.I.175.237; 5.I.175.238; 5.I.175.239; 5.I.175.154; 5.I.175.157; 5.I.175.166; 5.I.175.169; 5.I.175.172; 5.I.175.175; 5.I.175.240; 5.I.175.244; 5.I.240.228; 5.I.240.229; 5.I.240.230; 5.I.240.231;

5.I.240.236; 5.I.240.237; 5.I.240.238; 5.I.240.239; 5.I.240.154; 5.I.240.157; 5.I.240.166; 5.I.240.169; 5.I.240.172; 5.I.240.175; 5.I.240.240; 5.I.240.244; 5.I.244.228; 5.I.244.229; 5.I.244.230; 5.I.244.231; 5.I.244.236; 5.I.244.237; 5.I.244.238; 5.I.244.239; 5.I.244.154; 5.I.244.157; 5.I.244.166; 5.I.244.169; 5.I.244.172; 5.I.244.175; 5.I.244.240; 5.I.244.244;

Prodrugs of 5.J

5.J.228.228; 5.J.228.229; 5.J.228.230; 5.J.228.231; 5.J.228.236; 5.J.228.237; 5.J.228.238; 5.J.228.239; 5.J.228.154; 5.J.228.157; 5.J.228.166; 5.J.228.169; 5.J.228.172; 5.J.228.175; 5.J.228.240; 5.J.228.244; 5.J.229.228; 5.J.229.229; 5.J.229.230; 5.J.229.231; 5.J.229.236; 5.J.229.237; 5.J.229.238; 5.J.229.239; 5.J.229.154; 5.J.229.157; 5.J.229.166; 5.J.229.169; 5.J.229.172; 5.J.229.175; 5.J.229.240; 5.J.229.244; 5.J.230.228; 5.J.230.229; 5.J.230.230; 5.J.230.231; 5.J.230.236; 5.J.230.237; 5.J.230.238; 5.J.230.239; 5.J.230.154; 5.J.230.157; 5.J.230.166; 5.J.230.169; 5.J.230.172; 5.J.230.175; 5.J.230.240; 5.J.230.244; 5.J.231.228; 5.J.231.229; 5.J.231.230; 5.J.231.231; 5.J.231.236; 5.J.231.237; 5.J.231.238; 5.J.231.239; 5.J.231.154; 5.J.231.157; 5.J.231.166; 5.J.231.169; 5.J.231.172; 5.J.231.175; 5.J.231.240; 5.J.231.244; 5.J.236.228; 5.J.236.229; 5.J.236.230; 5.J.236.231; 5.J.236.236; 5.J.236.237; 5.J.236.238; 5.J.236.239; 5.J.236.154; 5.J.236.157; 5.J.236.166; 5.J.236.169; 5.J.236.172; 5.J.236.175; 5.J.236.240; 5.J.236.244; 5.J.237.228; 5.J.237.229; 5.J.237.230; 5.J.237.231; 5.J.237.236; 5.J.237.237; 5.J.237.238; 5.J.237.239; 5.J.237.154; 5.J.237.157; 5.J.237.166; 5.J.237.169; 5.J.237.172; 5.J.237.175; 5.J.237.240; 5.J.237.244; 5.J.238.228; 5.J.238.229; 5.J.238.230; 5.J.238.231; 5.J.238.236; 5.J.238.237; 5.J.238.238; 5.J.238.239; 5.J.238.154; 5.J.238.157; 5.J.238.166; 5.J.238.169; 5.J.238.172; 5.J.238.175; 5.J.238.240; 5.J.238.244; 5.J.239.228; 5.J.239.229; 5.J.239.230; 5.J.239.231; 5.J.239.236; 5.J.239.237; 5.J.239.238; 5.J.239.239; 5.J.239.154; 5.J.239.157; 5.J.239.166; 5.J.239.169; 5.J.239.172; 5.J.239.175; 5.J.239.240; 5.J.239.244; 5.J.154.228; 5.J.154.229; 5.J.154.230; 5.J.154.231; 5.J.154.236; 5.J.154.237; 5.J.154.238; 5.J.154.239; 5.J.154.154; 5.J.154.157;

5.J.154.166; 5.J.154.169; 5.J.154.172; 5.J.154.175; 5.J.154.240; 5.J.154.244; 5.J.157.228; 5.J.157.229; 5.J.157.230; 5.J.157.231; 5.J.157.236; 5.J.157.237; 5.J.157.238; 5.J.157.239; 5.J.157.154; 5.J.157.157; 5.J.157.166; 5.J.157.169; 5.J.157.172; 5.J.157.175; 5.J.157.240; 5.J.157.244; 5.J.166.228; 5.J.166.229; 5.J.166.230; 5.J.166.231; 5.J.166.236; 5.J.166.237; 5.J.166.238; 5.J.166.239; 5.J.166.154; 5.J.166.157; 5.J.166.166; 5.J.166.169; 5.J.166.172; 5.J.166.175; 5.J.166.240; 5.J.166.244; 5.J.169.228; 5.J.169.229; 5.J.169.230; 5.J.169.231; 5.J.169.236; 5.J.169.237; 5.J.169.238; 5.J.169.239; 5.J.169.154; 5.J.169.157; 5.J.169.166; 5.J.169.169; 5.J.169.172; 5.J.169.175; 5.J.169.240; 5.J.169.244; 5.J.172.228; 5.J.172.229; 5.J.172.230; 5.J.172.231; 5.J.172.236; 5.J.172.237; 5.J.172.238; 5.J.172.239; 5.J.172.154; 5.J.172.157; 5.J.172.166; 5.J.172.169; 5.J.172.172; 5.J.172.175; 5.J.172.240; 5.J.172.244; 5.J.175.228; 5.J.175.229; 5.J.175.230; 5.J.175.231; 5.J.175.236; 5.J.175.237; 5.J.175.238; 5.J.175.239; 5.J.175.154; 5.J.175.157; 5.J.175.166; 5.J.175.169; 5.J.175.172; 5.J.175.175; 5.J.175.240; 5.J.175.244; 5.J.240.228; 5.J.240.229; 5.J.240.230; 5.J.240.231; 5.J.240.236; 5.J.240.237; 5.J.240.238; 5.J.240.239; 5.J.240.154; 5.J.240.157; 5.J.240.166; 5.J.240.169; 5.J.240.172; 5.J.240.175; 5.J.240.240; 5.J.240.244; 5.J.244.228; 5.J.244.229; 5.J.244.230; 5.J.244.231; 5.J.244.236; 5.J.244.237; 5.J.244.238; 5.J.244.239; 5.J.244.154; 5.J.244.157; 5.J.244.166; 5.J.244.169; 5.J.244.172; 5.J.244.175; 5.J.244.240; 5.J.244.244;

Prodrugs of 5.L

5.L.228.228; 5.L.228.229; 5.L.228.230; 5.L.228.231; 5.L.228.236; 5.L.228.237; 5.L.228.238; 5.L.228.239; 5.L.228.154; 5.L.228.157; 5.L.228.166; 5.L.228.169; 5.L.228.172; 5.L.228.175; 5.L.228.240; 5.L.228.244; 5.L.229.228; 5.L.229.229; 5.L.229.230; 5.L.229.231; 5.L.229.236; 5.L.229.237; 5.L.229.238; 5.L.229.239; 5.L.229.154; 5.L.229.157; 5.L.229.166; 5.L.229.169; 5.L.229.172; 5.L.229.175; 5.L.229.240; 5.L.229.244; 5.L.230.228; 5.L.230.229; 5.L.230.230; 5.L.230.231; 5.L.230.236; 5.L.230.237; 5.L.230.238; 5.L.230.239; 5.L.230.154; 5.L.230.157; 5.L.230.166; 5.L.230.169; 5.L.230.172; 5.L.230.175; 5.L.230.240;

5.L.230.244; 5.L.231.228; 5.L.231.229; 5.L.231.230; 5.L.231.231; 5.L.231.236; 5.L.231.237; 5.L.231.238; 5.L.231.239; 5.L.231.154; 5.L.231.157; 5.L.231.166; 5.L.231.169; 5.L.231.172; 5.L.231.175; 5.L.231.240; 5.L.231.244; 5.L.236.228; 5.L.236.229; 5.L.236.230; 5.L.236.231; 5.L.236.236; 5.L.236.237; 5.L.236.238; 5.L.236.239; 5.L.236.154; 5.L.236.157; 5.L.236.166; 5.L.236.169; 5.L.236.172; 5.L.236.175; 5.L.236.240; 5.L.236.244; 5.L.237.228; 5.L.237.229; 5.L.237.230; 5.L.237.231; 5.L.237.236; 5.L.237.237; 5.L.237.238; 5.L.237.239; 5.L.237.154; 5.L.237.157; 5.L.237.166; 5.L.237.169; 5.L.237.172; 5.L.237.175; 5.L.237.240; 5.L.237.244; 5.L.238.228; 5.L.238.229; 5.L.238.230; 5.L.238.231; 5.L.238.236; 5.L.238.237; 5.L.238.238; 5.L.238.239; 5.L.238.154; 5.L.238.157; 5.L.238.166; 5.L.238.169; 5.L.238.172; 5.L.238.175; 5.L.238.240; 5.L.238.244; 5.L.239.228; 5.L.239.229; 5.L.239.230; 5.L.239.231; 5.L.239.236; 5.L.239.237; 5.L.239.238; 5.L.239.239; 5.L.239.154; 5.L.239.157; 5.L.239.166; 5.L.239.169; 5.L.239.172; 5.L.239.175; 5.L.239.240; 5.L.239.244; 5.L.154.228; 5.L.154.229; 5.L.154.230; 5.L.154.231; 5.L.154.236; 5.L.154.237; 5.L.154.238; 5.L.154.239; 5.L.154.154; 5.L.154.157; 5.L.154.166; 5.L.154.169; 5.L.154.172; 5.L.154.175; 5.L.154.240; 5.L.154.244; 5.L.157.228; 5.L.157.229; 5.L.157.230; 5.L.157.231; 5.L.157.236; 5.L.157.237; 5.L.157.238; 5.L.157.239; 5.L.157.154; 5.L.157.157; 5.L.157.166; 5.L.157.169; 5.L.157.172; 5.L.157.175; 5.L.157.240; 5.L.157.244; 5.L.166.228; 5.L.166.229; 5.L.166.230; 5.L.166.231; 5.L.166.236; 5.L.166.237; 5.L.166.238; 5.L.166.239; 5.L.166.154; 5.L.166.157; 5.L.166.166; 5.L.166.169; 5.L.166.172; 5.L.166.175; 5.L.166.240; 5.L.166.244; 5.L.169.228; 5.L.169.229; 5.L.169.230; 5.L.169.231; 5.L.169.236; 5.L.169.237; 5.L.169.238; 5.L.169.239; 5.L.169.154; 5.L.169.157; 5.L.169.166; 5.L.169.169; 5.L.169.172; 5.L.169.175; 5.L.169.240; 5.L.169.244; 5.L.172.228; 5.L.172.229; 5.L.172.230; 5.L.172.231; 5.L.172.236; 5.L.172.237; 5.L.172.238; 5.L.172.239; 5.L.172.154; 5.L.172.157; 5.L.172.166; 5.L.172.169; 5.L.172.172; 5.L.172.175; 5.L.172.240; 5.L.172.244; 5.L.175.228; 5.L.175.229; 5.L.175.230; 5.L.175.231; 5.L.175.236; 5.L.175.237; 5.L.175.238; 5.L.175.239; 5.L.175.154; 5.L.175.157; 5.L.175.166; 5.L.175.169; 5.L.175.172; 5.L.175.175; 5.L.175.240; 5.L.175.244; 5.L.240.228; 5.L.240.229; 5.L.240.230;

5.L.240.231; 5.L.240.236; 5.L.240.237; 5.L.240.238; 5.L.240.239; 5.L.240.154; 5.L.240.157; 5.L.240.166; 5.L.240.169; 5.L.240.172; 5.L.240.175; 5.L.240.240; 5.L.240.244; 5.L.244.228; 5.L.244.229; 5.L.244.230; 5.L.244.231; 5.L.244.236; 5.L.244.237; 5.L.244.238; 5.L.244.239; 5.L.244.154; 5.L.244.157; 5.L.244.166; 5.L.244.169; 5.L.244.172; 5.L.244.175; 5.L.244.240; 5.L.244.244;

Prodrugs of 5.O

5.O.228.228; 5.O.228.229; 5.O.228.230; 5.O.228.231; 5.O.228.236; 5.O.228.237; 5.O.228.238; 5.O.228.239; 5.O.228.154; 5.O.228.157; 5.O.228.166; 5.O.228.169; 5.O.228.172; 5.O.228.175; 5.O.228.240; 5.O.228.244; 5.O.229.228; 5.O.229.229; 5.O.229.230; 5.O.229.231; 5.O.229.236; 5.O.229.237; 5.O.229.238; 5.O.229.239; 5.O.229.154; 5.O.229.157; 5.O.229.166; 5.O.229.169; 5.O.229.172; 5.O.229.175; 5.O.229.240; 5.O.229.244; 5.O.230.228; 5.O.230.229; 5.O.230.230; 5.O.230.231; 5.O.230.236; 5.O.230.237; 5.O.230.238; 5.O.230.239; 5.O.230.154; 5.O.230.157; 5.O.230.166; 5.O.230.169; 5.O.230.172; 5.O.230.175; 5.O.230.240; 5.O.230.244; 5.O.231.228; 5.O.231.229; 5.O.231.230; 5.O.231.231; 5.O.231.236; 5.O.231.237; 5.O.231.238; 5.O.231.239; 5.O.231.154; 5.O.231.157; 5.O.231.166; 5.O.231.169; 5.O.231.172; 5.O.231.175; 5.O.231.240; 5.O.231.244; 5.O.236.228; 5.O.236.229; 5.O.236.230; 5.O.236.231; 5.O.236.236; 5.O.236.237; 5.O.236.238; 5.O.236.239; 5.O.236.154; 5.O.236.157; 5.O.236.166; 5.O.236.169; 5.O.236.172; 5.O.236.175; 5.O.236.240; 5.O.236.244; 5.O.237.228; 5.O.237.229; 5.O.237.230; 5.O.237.231; 5.O.237.236; 5.O.237.237; 5.O.237.238; 5.O.237.239; 5.O.237.154; 5.O.237.157; 5.O.237.166; 5.O.237.169; 5.O.237.172; 5.O.237.175; 5.O.237.240; 5.O.237.244; 5.O.238.228; 5.O.238.229; 5.O.238.230; 5.O.238.231; 5.O.238.236; 5.O.238.237; 5.O.238.238; 5.O.238.239; 5.O.238.154; 5.O.238.157; 5.O.238.166; 5.O.238.169; 5.O.238.172; 5.O.238.175; 5.O.238.240; 5.O.238.244; 5.O.239.228; 5.O.239.229; 5.O.239.230;

5.O.239.231; 5.O.239.236; 5.O.239.237; 5.O.239.238; 5.O.239.239; 5.O.239.154; 5.O.239.157; 5.O.239.166; 5.O.239.169; 5.O.239.172; 5.O.239.175; 5.O.239.240; 5.O.239.244; 5.O.154.228; 5.O.154.229; 5.O.154.230; 5.O.154.231; 5.O.154.236; 5.O.154.237; 5.O.154.238; 5.O.154.239; 5.O.154.154; 5.O.154.157; 5.O.154.166; 5.O.154.169; 5.O.154.172; 5.O.154.175; 5.O.154.240; 5.O.154.244; 5.O.157.228; 5.O.157.229; 5.O.157.230; 5.O.157.231; 5.O.157.236; 5.O.157.237; 5.O.157.238; 5.O.157.239; 5.O.157.154; 5.O.157.157; 5.O.157.166; 5.O.157.169; 5.O.157.172; 5.O.157.175; 5.O.157.240; 5.O.157.244; 5.O.166.228; 5.O.166.229; 5.O.166.230; 5.O.166.231; 5.O.166.236; 5.O.166.237; 5.O.166.238; 5.O.166.239; 5.O.166.154; 5.O.166.157; 5.O.166.166; 5.O.166.169; 5.O.166.172; 5.O.166.175; 5.O.166.240; 5.O.166.244; 5.O.169.228; 5.O.169.229; 5.O.169.230; 5.O.169.231; 5.O.169.236; 5.O.169.237; 5.O.169.238; 5.O.169.239; 5.O.169.154; 5.O.169.157; 5.O.169.166; 5.O.169.169; 5.O.169.172; 5.O.169.175; 5.O.169.240; 5.O.169.244; 5.O.172.228; 5.O.172.229; 5.O.172.230; 5.O.172.231; 5.O.172.236; 5.O.172.237; 5.O.172.238; 5.O.172.239; 5.O.172.154; 5.O.172.157; 5.O.172.166; 5.O.172.169; 5.O.172.172; 5.O.172.175; 5.O.172.240; 5.O.172.244; 5.O.175.228; 5.O.175.229; 5.O.175.230; 5.O.175.231; 5.O.175.236; 5.O.175.237; 5.O.175.238; 5.O.175.239; 5.O.175.154; 5.O.175.157; 5.O.175.166; 5.O.175.169; 5.O.175.172; 5.O.175.175; 5.O.175.240; 5.O.175.244; 5.O.240.228; 5.O.240.229; 5.O.240.230; 5.O.240.231; 5.O.240.236; 5.O.240.237; 5.O.240.238; 5.O.240.239; 5.O.240.154; 5.O.240.157; 5.O.240.166; 5.O.240.169; 5.O.240.172; 5.O.240.175; 5.O.240.240; 5.O.240.244; 5.O.244.228; 5.O.244.229; 5.O.244.230; 5.O.244.231; 5.O.244.236; 5.O.244.237; 5.O.244.238; 5.O.244.239; 5.O.244.154; 5.O.244.157; 5.O.244.166; 5.O.244.169; 5.O.244.172; 5.O.244.175; 5.O.244.240; 5.O.244.244;

Prodrugs of 5.P

5.P.228.228; 5.P.228.229; 5.P.228.230; 5.P.228.231; 5.P.228.236; 5.P.228.237; 5.P.228.238; 5.P.228.239; 5.P.228.154; 5.P.228.157; 5.P.228.166; 5.P.228.169; 5.P.228.172; 5.P.228.175; 5.P.228.240; 5.P.228.244; 5.P.229.228; 5.P.229.229; 5.P.229.230; 5.P.229.231; 5.P.229.236; 5.P.229.237; 5.P.229.238; 5.P.229.239; 5.P.229.154; 5.P.229.157; 5.P.229.166; 5.P.229.169; 5.P.229.172; 5.P.229.175; 5.P.229.240; 5.P.229.244; 5.P.230.228; 5.P.230.229; 5.P.230.230; 5.P.230.231; 5.P.230.236; 5.P.230.237; 5.P.230.238; 5.P.230.239; 5.P.230.154; 5.P.230.157; 5.P.230.166; 5.P.230.169; 5.P.230.172; 5.P.230.175; 5.P.230.240; 5.P.230.244; 5.P.231.228; 5.P.231.229; 5.P.231.230; 5.P.231.231; 5.P.231.236; 5.P.231.237; 5.P.231.238; 5.P.231.239; 5.P.231.154; 5.P.231.157; 5.P.231.166; 5.P.231.169; 5.P.231.172; 5.P.231.175; 5.P.231.240; 5.P.231.244; 5.P.236.228; 5.P.236.229; 5.P.236.230; 5.P.236.231; 5.P.236.236; 5.P.236.237; 5.P.236.238; 5.P.236.239; 5.P.236.154; 5.P.236.157; 5.P.236.166; 5.P.236.169; 5.P.236.172; 5.P.236.175; 5.P.236.240; 5.P.236.244; 5.P.237.228; 5.P.237.229; 5.P.237.230; 5.P.237.231; 5.P.237.236; 5.P.237.237; 5.P.237.238; 5.P.237.239; 5.P.237.154; 5.P.237.157; 5.P.237.166; 5.P.237.169; 5.P.237.172; 5.P.237.175; 5.P.237.240; 5.P.237.244; 5.P.238.228; 5.P.238.229; 5.P.238.230; 5.P.238.231; 5.P.238.236; 5.P.238.237; 5.P.238.238; 5.P.238.239; 5.P.238.154; 5.P.238.157; 5.P.238.166; 5.P.238.169; 5.P.238.172; 5.P.238.175; 5.P.238.240; 5.P.238.244; 5.P.239.228; 5.P.239.229; 5.P.239.230; 5.P.239.231; 5.P.239.236; 5.P.239.237; 5.P.239.238; 5.P.239.239; 5.P.239.154; 5.P.239.157; 5.P.239.166; 5.P.239.169; 5.P.239.172; 5.P.239.175; 5.P.239.240; 5.P.239.244; 5.P.154.228; 5.P.154.229; 5.P.154.230; 5.P.154.231; 5.P.154.236; 5.P.154.237; 5.P.154.238; 5.P.154.239; 5.P.154.154; 5.P.154.157; 5.P.154.166; 5.P.154.169; 5.P.154.172; 5.P.154.175; 5.P.154.240; 5.P.154.244; 5.P.157.228; 5.P.157.229; 5.P.157.230; 5.P.157.231; 5.P.157.236; 5.P.157.237; 5.P.157.238; 5.P.157.239; 5.P.157.154; 5.P.157.157; 5.P.157.166; 5.P.157.169; 5.P.157.172; 5.P.157.175; 5.P.157.240; 5.P.157.244; 5.P.166.228; 5.P.166.229; 5.P.166.230; 5.P.166.231; 5.P.166.236; 5.P.166.237; 5.P.166.238; 5.P.166.239; 5.P.166.154; 5.P.166.157; 5.P.166.166; 5.P.166.169; 5.P.166.172;

5.P.166.175; 5.P.166.240; 5.P.166.244; 5.P.169.228; 5.P.169.229; 5.P.169.230; 5.P.169.231; 5.P.169.236; 5.P.169.237; 5.P.169.238; 5.P.169.239; 5.P.169.154; 5.P.169.157; 5.P.169.166; 5.P.169.169; 5.P.169.172; 5.P.169.175; 5.P.169.240; 5.P.169.244; 5.P.172.228; 5.P.172.229; 5.P.172.230; 5.P.172.231; 5.P.172.236; 5.P.172.237; 5.P.172.238; 5.P.172.239; 5.P.172.154; 5.P.172.157; 5.P.172.166; 5.P.172.169; 5.P.172.172; 5.P.172.175; 5.P.172.240; 5.P.172.244; 5.P.175.228; 5.P.175.229; 5.P.175.230; 5.P.175.231; 5.P.175.236; 5.P.175.237; 5.P.175.238; 5.P.175.239; 5.P.175.154; 5.P.175.157; 5.P.175.166; 5.P.175.169; 5.P.175.172; 5.P.175.175; 5.P.175.240; 5.P.175.244; 5.P.240.228; 5.P.240.229; 5.P.240.230; 5.P.240.231; 5.P.240.236; 5.P.240.237; 5.P.240.238; 5.P.240.239; 5.P.240.154; 5.P.240.157; 5.P.240.166; 5.P.240.169; 5.P.240.172; 5.P.240.175; 5.P.240.240; 5.P.240.244; 5.P.244.228; 5.P.244.229; 5.P.244.230; 5.P.244.231; 5.P.244.236; 5.P.244.237; 5.P.244.238; 5.P.244.239; 5.P.244.154; 5.P.244.157; 5.P.244.166; 5.P.244.169; 5.P.244.172; 5.P.244.175; 5.P.244.240; 5.P.244.244;

Prodrugs of 5.U

5.U.228.228; 5.U.228.229; 5.U.228.230; 5.U.228.231; 5.U.228.236; 5.U.228.237; 5.U.228.238; 5.U.228.239; 5.U.228.154; 5.U.228.157; 5.U.228.166; 5.U.228.169; 5.U.228.172; 5.U.228.175; 5.U.228.240; 5.U.228.244; 5.U.229.228; 5.U.229.229; 5.U.229.230; 5.U.229.231; 5.U.229.236; 5.U.229.237; 5.U.229.238; 5.U.229.239; 5.U.229.154; 5.U.229.157; 5.U.229.166; 5.U.229.169; 5.U.229.172; 5.U.229.175; 5.U.229.240; 5.U.229.244; 5.U.230.228; 5.U.230.229; 5.U.230.230; 5.U.230.231; 5.U.230.236; 5.U.230.237; 5.U.230.238; 5.U.230.239; 5.U.230.154; 5.U.230.157; 5.U.230.166; 5.U.230.169; 5.U.230.172; 5.U.230.175; 5.U.230.240; 5.U.230.244; 5.U.231.228; 5.U.231.229; 5.U.231.230; 5.U.231.231; 5.U.231.236; 5.U.231.237; 5.U.231.238; 5.U.231.239; 5.U.231.154; 5.U.231.157; 5.U.231.166; 5.U.231.169; 5.U.231.172; 5.U.231.175; 5.U.231.240; 5.U.231.244; 5.U.236.228; 5.U.236.229; 5.U.236.230; 5.U.236.231; 5.U.236.236; 5.U.236.237;

5.U.236.238; 5.U.236.239; 5.U.236.154; 5.U.236.157; 5.U.236.166; 5.U.236.169; 5.U.236.172; 5.U.236.175; 5.U.236.240; 5.U.236.244; 5.U.237.228; 5.U.237.229; 5.U.237.230; 5.U.237.231; 5.U.237.236; 5.U.237.237; 5.U.237.238; 5.U.237.239; 5.U.237.154; 5.U.237.157; 5.U.237.166; 5.U.237.169; 5.U.237.172; 5.U.237.175; 5.U.237.240; 5.U.237.244; 5.U.238.228; 5.U.238.229; 5.U.238.230; 5.U.238.231; 5.U.238.236; 5.U.238.237; 5.U.238.238; 5.U.238.239; 5.U.238.154; 5.U.238.157; 5.U.238.166; 5.U.238.169; 5.U.238.172; 5.U.238.175; 5.U.238.240; 5.U.238.244; 5.U.239.228; 5.U.239.229; 5.U.239.230; 5.U.239.231; 5.U.239.236; 5.U.239.237; 5.U.239.238; 5.U.239.239; 5.U.239.154; 5.U.239.157; 5.U.239.166; 5.U.239.169; 5.U.239.172; 5.U.239.175; 5.U.239.240; 5.U.239.244; 5.U.154.228; 5.U.154.229; 5.U.154.230; 5.U.154.231; 5.U.154.236; 5.U.154.237; 5.U.154.238; 5.U.154.239; 5.U.154.154; 5.U.154.157; 5.U.154.166; 5.U.154.169; 5.U.154.172; 5.U.154.175; 5.U.154.240; 5.U.154.244; 5.U.157.228; 5.U.157.229; 5.U.157.230; 5.U.157.231; 5.U.157.236; 5.U.157.237; 5.U.157.238; 5.U.157.239; 5.U.157.154; 5.U.157.157; 5.U.157.166; 5.U.157.169; 5.U.157.172; 5.U.157.175; 5.U.157.240; 5.U.157.244; 5.U.166.228; 5.U.166.229; 5.U.166.230; 5.U.166.231; 5.U.166.236; 5.U.166.237; 5.U.166.238; 5.U.166.239; 5.U.166.154; 5.U.166.157; 5.U.166.166; 5.U.166.169; 5.U.166.172; 5.U.166.175; 5.U.166.240; 5.U.166.244; 5.U.169.228; 5.U.169.229; 5.U.169.230; 5.U.169.231; 5.U.169.236; 5.U.169.237; 5.U.169.238; 5.U.169.239; 5.U.169.154; 5.U.169.157; 5.U.169.166; 5.U.169.169; 5.U.169.172; 5.U.169.175; 5.U.169.240; 5.U.169.244; 5.U.172.228; 5.U.172.229; 5.U.172.230; 5.U.172.231; 5.U.172.236; 5.U.172.237; 5.U.172.238; 5.U.172.239; 5.U.172.154; 5.U.172.157; 5.U.172.166; 5.U.172.169; 5.U.172.172; 5.U.172.175; 5.U.172.240; 5.U.172.244; 5.U.175.228; 5.U.175.229; 5.U.175.230; 5.U.175.231; 5.U.175.236; 5.U.175.237; 5.U.175.238; 5.U.175.239; 5.U.175.154; 5.U.175.157; 5.U.175.166; 5.U.175.169;

5.U.175.172; 5.U.175.175; 5.U.175.240; 5.U.175.244; 5.U.240.228; 5.U.240.229; 5.U.240.230; 5.U.240.231; 5.U.240.236; 5.U.240.237; 5.U.240.238; 5.U.240.239; 5.U.240.154; 5.U.240.157; 5.U.240.166; 5.U.240.169; 5.U.240.172; 5.U.240.175; 5.U.240.240; 5.U.240.244; 5.U.244.228; 5.U.244.229; 5.U.244.230; 5.U.244.231; 5.U.244.236; 5.U.244.237; 5.U.244.238; 5.U.244.239; 5.U.244.154; 5.U.244.157; 5.U.244.166; 5.U.244.169; 5.U.244.172; 5.U.244.175; 5.U.244.240; 5.U.244.244;

Prodrugs of 5.W

5.W.228.228; 5.W.228.229; 5.W.228.230; 5.W.228.231; 5.W.228.236; 5.W.228.237; 5.W.228.238; 5.W.228.239; 5.W.228.154; 5.W.228.157; 5.W.228.166; 5.W.228.169; 5.W.228.172; 5.W.228.175; 5.W.228.240; 5.W.228.244; 5.W.229.228; 5.W.229.229; 5.W.229.230; 5.W.229.231; 5.W.229.236; 5.W.229.237; 5.W.229.238; 5.W.229.239; 5.W.229.154; 5.W.229.157; 5.W.229.166; 5.W.229.169; 5.W.229.172; 5.W.229.175; 5.W.229.240; 5.W.229.244; 5.W.230.228; 5.W.230.229; 5.W.230.230; 5.W.230.231; 5.W.230.236; 5.W.230.237; 5.W.230.238; 5.W.230.239; 5.W.230.154; 5.W.230.157; 5.W.230.166; 5.W.230.169; 5.W.230.172; 5.W.230.175; 5.W.230.240; 5.W.230.244; 5.W.231.228; 5.W.231.229; 5.W.231.230; 5.W.231.231; 5.W.231.236; 5.W.231.237; 5.W.231.238; 5.W.231.239; 5.W.231.154; 5.W.231.157; 5.W.231.166; 5.W.231.169; 5.W.231.172; 5.W.231.175; 5.W.231.240; 5.W.231.244; 5.W.236.228; 5.W.236.229; 5.W.236.230; 5.W.236.231; 5.W.236.236; 5.W.236.237; 5.W.236.238; 5.W.236.239; 5.W.236.154; 5.W.236.157; 5.W.236.166; 5.W.236.169; 5.W.236.172; 5.W.236.175; 5.W.236.240; 5.W.236.244; 5.W.237.228; 5.W.237.229; 5.W.237.230; 5.W.237.231; 5.W.237.236; 5.W.237.237; 5.W.237.238; 5.W.237.239; 5.W.237.154; 5.W.237.157; 5.W.237.166; 5.W.237.169; 5.W.237.172; 5.W.237.175; 5.W.237.240; 5.W.237.244; 5.W.238.228; 5.W.238.229; 5.W.238.230; 5.W.238.231;

5.W.238.236; 5.W.238.237; 5.W.238.238; 5.W.238.239; 5.W.238.154; 5.W.238.157; 5.W.238.166; 5.W.238.169; 5.W.238.172; 5.W.238.175; 5.W.238.240; 5.W.238.244; 5.W.239.228; 5.W.239.229; 5.W.239.230; 5.W.239.231; 5.W.239.236; 5.W.239.237; 5.W.239.238; 5.W.239.239; 5.W.239.154; 5.W.239.157; 5.W.239.166; 5.W.239.169; 5.W.239.172; 5.W.239.175; 5.W.239.240; 5.W.239.244; 5.W.154.228; 5.W.154.229; 5.W.154.230; 5.W.154.231; 5.W.154.236; 5.W.154.237; 5.W.154.238; 5.W.154.239; 5.W.154.154; 5.W.154.157; 5.W.154.166; 5.W.154.169; 5.W.154.172; 5.W.154.175; 5.W.154.240; 5.W.154.244; 5.W.157.228; 5.W.157.229; 5.W.157.230; 5.W.157.231; 5.W.157.236; 5.W.157.237; 5.W.157.238; 5.W.157.239; 5.W.157.154; 5.W.157.157; 5.W.157.166; 5.W.157.169; 5.W.157.172; 5.W.157.175; 5.W.157.240; 5.W.157.244; 5.W.166.228; 5.W.166.229; 5.W.166.230; 5.W.166.231; 5.W.166.236; 5.W.166.237; 5.W.166.238; 5.W.166.239; 5.W.166.154; 5.W.166.157; 5.W.166.166; 5.W.166.169; 5.W.166.172; 5.W.166.175; 5.W.166.240; 5.W.166.244; 5.W.169.228; 5.W.169.229; 5.W.169.230; 5.W.169.231; 5.W.169.236; 5.W.169.237; 5.W.169.238; 5.W.169.239; 5.W.169.154; 5.W.169.157; 5.W.169.166; 5.W.169.169; 5.W.169.172; 5.W.169.175; 5.W.169.240; 5.W.169.244; 5.W.172.228; 5.W.172.229; 5.W.172.230; 5.W.172.231; 5.W.172.236; 5.W.172.237; 5.W.172.238; 5.W.172.239; 5.W.172.154; 5.W.172.157; 5.W.172.166; 5.W.172.169; 5.W.172.172; 5.W.172.175; 5.W.172.240; 5.W.172.244; 5.W.175.228; 5.W.175.229; 5.W.175.230; 5.W.175.231; 5.W.175.236; 5.W.175.237; 5.W.175.238; 5.W.175.239; 5.W.175.154; 5.W.175.157; 5.W.175.166; 5.W.175.169; 5.W.175.172; 5.W.175.175; 5.W.175.240; 5.W.175.244; 5.W.240.228; 5.W.240.229; 5.W.240.230; 5.W.240.231; 5.W.240.236; 5.W.240.237; 5.W.240.238; 5.W.240.239; 5.W.240.154; 5.W.240.157; 5.W.240.166; 5.W.240.169; 5.W.240.172; 5.W.240.175; 5.W.240.240; 5.W.240.244; 5.W.244.228; 5.W.244.229; 5.W.244.230; 5.W.244.231; 5.W.244.236; 5.W.244.237; 5.W.244.238; 5.W.244.239; 5.W.244.154; 5.W.244.157;

5.W.244.166; 5.W.244.169; 5.W.244.172; 5.W.244.175; 5.W.244.240; 5.W.244.244;

Prodrugs of 5.Y

5.Y.228.228; 5.Y.228.229; 5.Y.228.230; 5.Y.228.231; 5.Y.228.236; 5.Y.228.237; 5.Y.228.238; 5.Y.228.239; 5.Y.228.154; 5.Y.228.157; 5.Y.228.166; 5.Y.228.169; 5.Y.228.172; 5.Y.228.175; 5.Y.228.240; 5.Y.228.244; 5.Y.229.228; 5.Y.229.229; 5.Y.229.230; 5.Y.229.231; 5.Y.229.236; 5.Y.229.237; 5.Y.229.238; 5.Y.229.239; 5.Y.229.154; 5.Y.229.157; 5.Y.229.166; 5.Y.229.169; 5.Y.229.172; 5.Y.229.175; 5.Y.229.240; 5.Y.229.244; 5.Y.230.228; 5.Y.230.229; 5.Y.230.230; 5.Y.230.231; 5.Y.230.236; 5.Y.230.237; 5.Y.230.238; 5.Y.230.239; 5.Y.230.154; 5.Y.230.157; 5.Y.230.166; 5.Y.230.169; 5.Y.230.172; 5.Y.230.175; 5.Y.230.240; 5.Y.230.244; 5.Y.231.228; 5.Y.231.229; 5.Y.231.230; 5.Y.231.231; 5.Y.231.236; 5.Y.231.237; 5.Y.231.238; 5.Y.231.239; 5.Y.231.154; 5.Y.231.157; 5.Y.231.166; 5.Y.231.169; 5.Y.231.172; 5.Y.231.175; 5.Y.231.240; 5.Y.231.244; 5.Y.236.228; 5.Y.236.229; 5.Y.236.230; 5.Y.236.231; 5.Y.236.236; 5.Y.236.237; 5.Y.236.238; 5.Y.236.239; 5.Y.236.154; 5.Y.236.157; 5.Y.236.166; 5.Y.236.169; 5.Y.236.172; 5.Y.236.175; 5.Y.236.240; 5.Y.236.244; 5.Y.237.228; 5.Y.237.229; 5.Y.237.230; 5.Y.237.231; 5.Y.237.236; 5.Y.237.237; 5.Y.237.238; 5.Y.237.239; 5.Y.237.154; 5.Y.237.157; 5.Y.237.166; 5.Y.237.169; 5.Y.237.172; 5.Y.237.175; 5.Y.237.240; 5.Y.237.244; 5.Y.238.228; 5.Y.238.229; 5.Y.238.230; 5.Y.238.231; 5.Y.238.236; 5.Y.238.237; 5.Y.238.238; 5.Y.238.239; 5.Y.238.154; 5.Y.238.157; 5.Y.238.166; 5.Y.238.169; 5.Y.238.172; 5.Y.238.175; 5.Y.238.240; 5.Y.238.244; 5.Y.239.228; 5.Y.239.229; 5.Y.239.230; 5.Y.239.231; 5.Y.239.236; 5.Y.239.237; 5.Y.239.238; 5.Y.239.239; 5.Y.239.154; 5.Y.239.157; 5.Y.239.166; 5.Y.239.169; 5.Y.239.172; 5.Y.239.175; 5.Y.239.240; 5.Y.239.244; 5.Y.154.228; 5.Y.154.229; 5.Y.154.230; 5.Y.154.231; 5.Y.154.236; 5.Y.154.237; 5.Y.154.238; 5.Y.154.239; 5.Y.154.154; 5.Y.154.157; 5.Y.154.166; 5.Y.154.169; 5.Y.154.172; 5.Y.154.175; 5.Y.154.240; 5.Y.154.244; 5.Y.157.228; 5.Y.157.229; 5.Y.157.230; 5.Y.157.231; 5.Y.157.236; 5.Y.157.237; 5.Y.157.238; 5.Y.157.239; 5.Y.157.154; 5.Y.157.157; 5.Y.157.166;

5.Y.157.169; 5.Y.157.172; 5.Y.157.175; 5.Y.157.240; 5.Y.157.244; 5.Y.166.228; 5.Y.166.229; 5.Y.166.230; 5.Y.166.231; 5.Y.166.236; 5.Y.166.237; 5.Y.166.238; 5.Y.166.239; 5.Y.166.154; 5.Y.166.157; 5.Y.166.166; 5.Y.166.169; 5.Y.166.172; 5.Y.166.175; 5.Y.166.240; 5.Y.166.244; 5.Y.169.228; 5.Y.169.229; 5.Y.169.230; 5.Y.169.231; 5.Y.169.236; 5.Y.169.237; 5.Y.169.238; 5.Y.169.239; 5.Y.169.154; 5.Y.169.157; 5.Y.169.166; 5.Y.169.169; 5.Y.169.172; 5.Y.169.175; 5.Y.169.240; 5.Y.169.244; 5.Y.172.228; 5.Y.172.229; 5.Y.172.230; 5.Y.172.231; 5.Y.172.236; 5.Y.172.237; 5.Y.172.238; 5.Y.172.239; 5.Y.172.154; 5.Y.172.157; 5.Y.172.166; 5.Y.172.169; 5.Y.172.172; 5.Y.172.175; 5.Y.172.240; 5.Y.172.244; 5.Y.175.228; 5.Y.175.229; 5.Y.175.230; 5.Y.175.231; 5.Y.175.236; 5.Y.175.237; 5.Y.175.238; 5.Y.175.239; 5.Y.175.154; 5.Y.175.157; 5.Y.175.166; 5.Y.175.169; 5.Y.175.172; 5.Y.175.175; 5.Y.175.240; 5.Y.175.244; 5.Y.240.228; 5.Y.240.229; 5.Y.240.230; 5.Y.240.231; 5.Y.240.236; 5.Y.240.237; 5.Y.240.238; 5.Y.240.239; 5.Y.240.154; 5.Y.240.157; 5.Y.240.166; 5.Y.240.169; 5.Y.240.172; 5.Y.240.175; 5.Y.240.240; 5.Y.240.244; 5.Y.244.228; 5.Y.244.229; 5.Y.244.230; 5.Y.244.231; 5.Y.244.236; 5.Y.244.237; 5.Y.244.238; 5.Y.244.239; 5.Y.244.154; 5.Y.244.157; 5.Y.244.166; 5.Y.244.169; 5.Y.244.172; 5.Y.244.175; 5.Y.244.240; 5.Y.244.244;

Prodrugs of 6.B

6.B.228.228; 6.B.228.229; 6.B.228.230; 6.B.228.231; 6.B.228.236; 6.B.228.237; 6.B.228.238; 6.B.228.239; 6.B.228.154; 6.B.228.157; 6.B.228.166; 6.B.228.169; 6.B.228.172; 6.B.228.175; 6.B.228.240; 6.B.228.244; 6.B.229.228; 6.B.229.229; 6.B.229.230; 6.B.229.231; 6.B.229.236; 6.B.229.237; 6.B.229.238; 6.B.229.239; 6.B.229.154; 6.B.229.157; 6.B.229.166; 6.B.229.169; 6.B.229.172; 6.B.229.175; 6.B.229.240; 6.B.229.244; 6.B.230.228; 6.B.230.229; 6.B.230.230; 6.B.230.231; 6.B.230.236; 6.B.230.237; 6.B.230.238; 6.B.230.239; 6.B.230.154; 6.B.230.157; 6.B.230.166; 6.B.230.169; 6.B.230.172; 6.B.230.175; 6.B.230.240; 6.B.230.244; 6.B.231.228; 6.B.231.229; 6.B.231.230; 6.B.231.231; 6.B.231.236; 6.B.231.237; 6.B.231.238; 6.B.231.239; 6.B.231.154; 6.B.231.157; 6.B.231.166; 6.B.231.169; 6.B.231.172; 6.B.231.175; 6.B.231.240; 6.B.231.244; 6.B.236.228;

6.B.236.229; 6.B.236.230; 6.B.236.231; 6.B.236.236; 6.B.236.237; 6.B.236.238; 6.B.236.239; 6.B.236.154; 6.B.236.157; 6.B.236.166; 6.B.236.169; 6.B.236.172; 6.B.236.175; 6.B.236.240; 6.B.236.244; 6.B.237.228; 6.B.237.229; 6.B.237.230; 6.B.237.231; 6.B.237.236; 6.B.237.237; 6.B.237.238; 6.B.237.239; 6.B.237.154; 6.B.237.157; 6.B.237.166; 6.B.237.169; 6.B.237.172; 6.B.237.175; 6.B.237.240; 6.B.237.244; 6.B.238.228; 6.B.238.229; 6.B.238.230; 6.B.238.231; 6.B.238.236; 6.B.238.237; 6.B.238.238; 6.B.238.239; 6.B.238.154; 6.B.238.157; 6.B.238.166; 6.B.238.169; 6.B.238.172; 6.B.238.175; 6.B.238.240; 6.B.238.244; 6.B.239.228; 6.B.239.229; 6.B.239.230; 6.B.239.231; 6.B.239.236; 6.B.239.237; 6.B.239.238; 6.B.239.239; 6.B.239.154; 6.B.239.157; 6.B.239.166; 6.B.239.169; 6.B.239.172; 6.B.239.175; 6.B.239.240; 6.B.239.244; 6.B.154.228; 6.B.154.229; 6.B.154.230; 6.B.154.231; 6.B.154.236; 6.B.154.237; 6.B.154.238; 6.B.154.239; 6.B.154.154; 6.B.154.157; 6.B.154.166; 6.B.154.169; 6.B.154.172; 6.B.154.175; 6.B.154.240; 6.B.154.244; 6.B.157.228; 6.B.157.229; 6.B.157.230; 6.B.157.231; 6.B.157.236; 6.B.157.237; 6.B.157.238; 6.B.157.239; 6.B.157.154; 6.B.157.157; 6.B.157.166; 6.B.157.169; 6.B.157.172; 6.B.157.175; 6.B.157.240; 6.B.157.244; 6.B.166.228; 6.B.166.229; 6.B.166.230; 6.B.166.231; 6.B.166.236; 6.B.166.237; 6.B.166.238; 6.B.166.239; 6.B.166.154; 6.B.166.157; 6.B.166.166; 6.B.166.169; 6.B.166.172; 6.B.166.175; 6.B.166.240; 6.B.166.244; 6.B.169.228; 6.B.169.229; 6.B.169.230; 6.B.169.231; 6.B.169.236; 6.B.169.237; 6.B.169.238; 6.B.169.239; 6.B.169.154; 6.B.169.157; 6.B.169.166; 6.B.169.169; 6.B.169.172; 6.B.169.175; 6.B.169.240; 6.B.169.244; 6.B.172.228; 6.B.172.229; 6.B.172.230; 6.B.172.231; 6.B.172.236; 6.B.172.237; 6.B.172.238; 6.B.172.239; 6.B.172.154; 6.B.172.157; 6.B.172.166; 6.B.172.169; 6.B.172.172; 6.B.172.175; 6.B.172.240; 6.B.172.244; 6.B.175.228; 6.B.175.229; 6.B.175.230; 6.B.175.231; 6.B.175.236; 6.B.175.237; 6.B.175.238; 6.B.175.239; 6.B.175.154; 6.B.175.157; 6.B.175.166; 6.B.175.169; 6.B.175.172; 6.B.175.175; 6.B.175.240; 6.B.175.244; 6.B.240.228; 6.B.240.229; 6.B.240.230; 6.B.240.231; 6.B.240.236; 6.B.240.237; 6.B.240.238; 6.B.240.239; 6.B.240.154; 6.B.240.157; 6.B.240.166; 6.B.240.169; 6.B.240.172; 6.B.240.175; 6.B.240.240; 6.B.240.244; 6.B.244.228; 6.B.244.229; 6.B.244.230; 6.B.244.231; 6.B.244.236;

6.B.244.237; 6.B.244.238; 6.B.244.239; 6.B.244.154; 6.B.244.157; 6.B.244.166; 6.B.244.169; 6.B.244.172; 6.B.244.175; 6.B.244.240; 6.B.244.244;

Prodrugs of 6.D

6.D.228.228; 6.D.228.229; 6.D.228.230; 6.D.228.231; 6.D.228.236; 6.D.228.237; 6.D.228.238; 6.D.228.239; 6.D.228.154; 6.D.228.157; 6.D.228.166; 6.D.228.169; 6.D.228.172; 6.D.228.175; 6.D.228.240; 6.D.228.244; 6.D.229.228; 6.D.229.229; 6.D.229.230; 6.D.229.231; 6.D.229.236; 6.D.229.237; 6.D.229.238; 6.D.229.239; 6.D.229.154; 6.D.229.157; 6.D.229.166; 6.D.229.169; 6.D.229.172; 6.D.229.175; 6.D.229.240; 6.D.229.244; 6.D.230.228; 6.D.230.229; 6.D.230.230; 6.D.230.231; 6.D.230.236; 6.D.230.237; 6.D.230.238; 6.D.230.239; 6.D.230.154; 6.D.230.157; 6.D.230.166; 6.D.230.169; 6.D.230.172; 6.D.230.175; 6.D.230.240; 6.D.230.244; 6.D.231.228; 6.D.231.229; 6.D.231.230; 6.D.231.231; 6.D.231.236; 6.D.231.237; 6.D.231.238; 6.D.231.239; 6.D.231.154; 6.D.231.157; 6.D.231.166; 6.D.231.169; 6.D.231.172; 6.D.231.175; 6.D.231.240; 6.D.231.244; 6.D.236.228; 6.D.236.229; 6.D.236.230; 6.D.236.231; 6.D.236.236; 6.D.236.237; 6.D.236.238; 6.D.236.239; 6.D.236.154; 6.D.236.157; 6.D.236.166; 6.D.236.169; 6.D.236.172; 6.D.236.175; 6.D.236.240; 6.D.236.244; 6.D.237.228; 6.D.237.229; 6.D.237.230; 6.D.237.231; 6.D.237.236; 6.D.237.237; 6.D.237.238; 6.D.237.239; 6.D.237.154; 6.D.237.157; 6.D.237.166; 6.D.237.169; 6.D.237.172; 6.D.237.175; 6.D.237.240; 6.D.237.244; 6.D.238.228; 6.D.238.229; 6.D.238.230; 6.D.238.231; 6.D.238.236; 6.D.238.237; 6.D.238.238; 6.D.238.239; 6.D.238.154; 6.D.238.157; 6.D.238.166; 6.D.238.169; 6.D.238.172; 6.D.238.175; 6.D.238.240; 6.D.238.244; 6.D.239.228; 6.D.239.229; 6.D.239.230; 6.D.239.231; 6.D.239.236; 6.D.239.237; 6.D.239.238; 6.D.239.239; 6.D.239.154; 6.D.239.157; 6.D.239.166; 6.D.239.169; 6.D.239.172; 6.D.239.175; 6.D.239.240; 6.D.239.244; 6.D.154.228; 6.D.154.229;

6.D.154.230; 6.D.154.231; 6.D.154.236; 6.D.154.237; 6.D.154.238; 6.D.154.239; 6.D.154.154; 6.D.154.157; 6.D.154.166; 6.D.154.169; 6.D.154.172; 6.D.154.175; 6.D.154.240; 6.D.154.244; 6.D.157.228; 6.D.157.229; 6.D.157.230; 6.D.157.231; 6.D.157.236; 6.D.157.237; 6.D.157.238; 6.D.157.239; 6.D.157.154; 6.D.157.157; 6.D.157.166; 6.D.157.169; 6.D.157.172; 6.D.157.175; 6.D.157.240; 6.D.157.244; 6.D.166.228; 6.D.166.229; 6.D.166.230; 6.D.166.231; 6.D.166.236; 6.D.166.237; 6.D.166.238; 6.D.166.239; 6.D.166.154; 6.D.166.157; 6.D.166.166; 6.D.166.169; 6.D.166.172; 6.D.166.175; 6.D.166.240; 6.D.166.244; 6.D.169.228; 6.D.169.229; 6.D.169.230; 6.D.169.231; 6.D.169.236; 6.D.169.237; 6.D.169.238; 6.D.169.239; 6.D.169.154; 6.D.169.157; 6.D.169.166; 6.D.169.169; 6.D.169.172; 6.D.169.175; 6.D.169.240; 6.D.169.244; 6.D.172.228; 6.D.172.229; 6.D.172.230; 6.D.172.231; 6.D.172.236; 6.D.172.237; 6.D.172.238; 6.D.172.239; 6.D.172.154; 6.D.172.157; 6.D.172.166; 6.D.172.169; 6.D.172.172; 6.D.172.175; 6.D.172.240; 6.D.172.244; 6.D.175.228; 6.D.175.229; 6.D.175.230; 6.D.175.231; 6.D.175.236; 6.D.175.237; 6.D.175.238; 6.D.175.239; 6.D.175.154; 6.D.175.157; 6.D.175.166; 6.D.175.169; 6.D.175.172; 6.D.175.175; 6.D.175.240; 6.D.175.244; 6.D.240.228; 6.D.240.229; 6.D.240.230; 6.D.240.231; 6.D.240.236; 6.D.240.237; 6.D.240.238; 6.D.240.239; 6.D.240.154; 6.D.240.157; 6.D.240.166; 6.D.240.169; 6.D.240.172; 6.D.240.175; 6.D.240.240; 6.D.240.244; 6.D.244.228; 6.D.244.229; 6.D.244.230; 6.D.244.231; 6.D.244.236; 6.D.244.237; 6.D.244.238; 6.D.244.239; 6.D.244.154; 6.D.244.157; 6.D.244.166; 6.D.244.169; 6.D.244.172; 6.D.244.175; 6.D.244.240; 6.D.244.244;

Prodrugs of 6.E

6.E.228.228; 6.E.228.229; 6.E.228.230; 6.E.228.231; 6.E.228.236; 6.E.228.237; 6.E.228.238; 6.E.228.239; 6.E.228.154; 6.E.228.157; 6.E.228.166;

6.E.228.169; 6.E.228.172; 6.E.228.175; 6.E.228.240; 6.E.228.244; 6.E.229.228; 6.E.229.229; 6.E.229.230; 6.E.229.231; 6.E.229.236; 6.E.229.237; 6.E.229.238; 6.E.229.239; 6.E.229.154; 6.E.229.157; 6.E.229.166; 6.E.229.169; 6.E.229.172; 6.E.229.175; 6.E.229.240; 6.E.229.244; 6.E.230.228; 6.E.230.229; 6.E.230.230; 6.E.230.231; 6.E.230.236; 6.E.230.237; 6.E.230.238; 6.E.230.239; 6.E.230.154; 6.E.230.157; 6.E.230.166; 6.E.230.169; 6.E.230.172; 6.E.230.175; 6.E.230.240; 6.E.230.244; 6.E.231.228; 6.E.231.229; 6.E.231.230; 6.E.231.231; 6.E.231.236; 6.E.231.237; 6.E.231.238; 6.E.231.239; 6.E.231.154; 6.E.231.157; 6.E.231.166; 6.E.231.169; 6.E.231.172; 6.E.231.175; 6.E.231.240; 6.E.231.244; 6.E.236.228; 6.E.236.229; 6.E.236.230; 6.E.236.231; 6.E.236.236; 6.E.236.237; 6.E.236.238; 6.E.236.239; 6.E.236.154; 6.E.236.157; 6.E.236.166; 6.E.236.169; 6.E.236.172; 6.E.236.175; 6.E.236.240; 6.E.236.244; 6.E.237.228; 6.E.237.229; 6.E.237.230; 6.E.237.231; 6.E.237.236; 6.E.237.237; 6.E.237.238; 6.E.237.239; 6.E.237.154; 6.E.237.157; 6.E.237.166; 6.E.237.169; 6.E.237.172; 6.E.237.175; 6.E.237.240; 6.E.237.244; 6.E.238.228; 6.E.238.229; 6.E.238.230; 6.E.238.231; 6.E.238.236; 6.E.238.237; 6.E.238.238; 6.E.238.239; 6.E.238.154; 6.E.238.157; 6.E.238.166; 6.E.238.169; 6.E.238.172; 6.E.238.175; 6.E.238.240; 6.E.238.244; 6.E.239.228; 6.E.239.229; 6.E.239.230; 6.E.239.231; 6.E.239.236; 6.E.239.237; 6.E.239.238; 6.E.239.239; 6.E.239.154; 6.E.239.157; 6.E.239.166; 6.E.239.169; 6.E.239.172; 6.E.239.175; 6.E.239.240; 6.E.239.244; 6.E.154.228; 6.E.154.229; 6.E.154.230; 6.E.154.231; 6.E.154.236; 6.E.154.237; 6.E.154.238; 6.E.154.239; 6.E.154.154; 6.E.154.157; 6.E.154.166; 6.E.154.169; 6.E.154.172; 6.E.154.175; 6.E.154.240; 6.E.154.244; 6.E.157.228; 6.E.157.229; 6.E.157.230; 6.E.157.231; 6.E.157.236; 6.E.157.237; 6.E.157.238; 6.E.157.239; 6.E.157.154; 6.E.157.157; 6.E.157.166; 6.E.157.169; 6.E.157.172; 6.E.157.175; 6.E.157.240; 6.E.157.244; 6.E.166.228; 6.E.166.229; 6.E.166.230; 6.E.166.231; 6.E.166.236; 6.E.166.237; 6.E.166.238; 6.E.166.239; 6.E.166.154; 6.E.166.157; 6.E.166.166; 6.E.166.169; 6.E.166.172; 6.E.166.175; 6.E.166.240; 6.E.166.244; 6.E.169.228; 6.E.169.229; 6.E.169.230; 6.E.169.231; 6.E.169.236; 6.E.169.237; 6.E.169.238; 6.E.169.239; 6.E.169.154; 6.E.169.157; 6.E.169.166; 6.E.169.169; 6.E.169.172; 6.E.169.175; 6.E.169.240;

6.E.169.244; 6.E.172.228; 6.E.172.229; 6.E.172.230; 6.E.172.231; 6.E.172.236; 6.E.172.237; 6.E.172.238; 6.E.172.239; 6.E.172.154; 6.E.172.157; 6.E.172.166; 6.E.172.169; 6.E.172.172; 6.E.172.175; 6.E.172.240; 6.E.172.244; 6.E.175.228; 6.E.175.229; 6.E.175.230; 6.E.175.231; 6.E.175.236; 6.E.175.237; 6.E.175.238; 6.E.175.239; 6.E.175.154; 6.E.175.157; 6.E.175.166; 6.E.175.169; 6.E.175.172; 6.E.175.175; 6.E.175.240; 6.E.175.244; 6.E.240.228; 6.E.240.229; 6.E.240.230; 6.E.240.231; 6.E.240.236; 6.E.240.237; 6.E.240.238; 6.E.240.239; 6.E.240.154; 6.E.240.157; 6.E.240.166; 6.E.240.169; 6.E.240.172; 6.E.240.175; 6.E.240.240; 6.E.240.244; 6.E.244.228; 6.E.244.229; 6.E.244.230; 6.E.244.231; 6.E.244.236; 6.E.244.237; 6.E.244.238; 6.E.244.239; 6.E.244.154; 6.E.244.157; 6.E.244.166; 6.E.244.169; 6.E.244.172; 6.E.244.175; 6.E.244.240; 6.E.244.244;

Prodrugs of 6.G

6.G.228.228; 6.G.228.229; 6.G.228.230; 6.G.228.231; 6.G.228.236; 6.G.228.237; 6.G.228.238; 6.G.228.239; 6.G.228.154; 6.G.228.157; 6.G.228.166; 6.G.228.169; 6.G.228.172; 6.G.228.175; 6.G.228.240; 6.G.228.244; 6.G.229.228; 6.G.229.229; 6.G.229.230; 6.G.229.231; 6.G.229.236; 6.G.229.237; 6.G.229.238; 6.G.229.239; 6.G.229.154; 6.G.229.157; 6.G.229.166; 6.G.229.169; 6.G.229.172; 6.G.229.175; 6.G.229.240; 6.G.229.244; 6.G.230.228; 6.G.230.229; 6.G.230.230; 6.G.230.231; 6.G.230.236; 6.G.230.237; 6.G.230.238; 6.G.230.239; 6.G.230.154; 6.G.230.157; 6.G.230.166; 6.G.230.169; 6.G.230.172; 6.G.230.175; 6.G.230.240; 6.G.230.244; 6.G.231.228; 6.G.231.229; 6.G.231.230; 6.G.231.231; 6.G.231.236; 6.G.231.237; 6.G.231.238; 6.G.231.239; 6.G.231.154; 6.G.231.157; 6.G.231.166; 6.G.231.169; 6.G.231.172; 6.G.231.175; 6.G.231.240; 6.G.231.244; 6.G.236.228; 6.G.236.229; 6.G.236.230; 6.G.236.231; 6.G.236.236; 6.G.236.237; 6.G.236.238; 6.G.236.239; 6.G.236.154; 6.G.236.157; 6.G.236.166; 6.G.236.169; 6.G.236.172; 6.G.236.175; 6.G.236.240; 6.G.236.244; 6.G.237.228; 6.G.237.229; 6.G.237.230; 6.G.237.231; 6.G.237.236;

6.G.237.237; 6.G.237.238; 6.G.237.239; 6.G.237.154; 6.G.237.157; 6.G.237.166; 6.G.237.169; 6.G.237.172; 6.G.237.175; 6.G.237.240; 6.G.237.244; 6.G.238.228; 6.G.238.229; 6.G.238.230; 6.G.238.231; 6.G.238.236; 6.G.238.237; 6.G.238.238; 6.G.238.239; 6.G.238.154; 6.G.238.157; 6.G.238.166; 6.G.238.169; 6.G.238.172; 6.G.238.175; 6.G.238.240; 6.G.238.244; 6.G.239.228; 6.G.239.229; 6.G.239.230; 6.G.239.231; 6.G.239.236; 6.G.239.237; 6.G.239.238; 6.G.239.239; 6.G.239.154; 6.G.239.157; 6.G.239.166; 6.G.239.169; 6.G.239.172; 6.G.239.175; 6.G.239.240; 6.G.239.244; 6.G.154.228; 6.G.154.229; 6.G.154.230; 6.G.154.231; 6.G.154.236; 6.G.154.237; 6.G.154.238; 6.G.154.239; 6.G.154.154; 6.G.154.157; 6.G.154.166; 6.G.154.169; 6.G.154.172; 6.G.154.175; 6.G.154.240; 6.G.154.244; 6.G.157.228; 6.G.157.229; 6.G.157.230; 6.G.157.231; 6.G.157.236; 6.G.157.237; 6.G.157.238; 6.G.157.239; 6.G.157.154; 6.G.157.157; 6.G.157.166; 6.G.157.169; 6.G.157.172; 6.G.157.175; 6.G.157.240; 6.G.157.244; 6.G.166.228; 6.G.166.229; 6.G.166.230; 6.G.166.231; 6.G.166.236; 6.G.166.237; 6.G.166.238; 6.G.166.239; 6.G.166.154; 6.G.166.157; 6.G.166.166; 6.G.166.169; 6.G.166.172; 6.G.166.175; 6.G.166.240; 6.G.166.244; 6.G.169.228; 6.G.169.229; 6.G.169.230; 6.G.169.231; 6.G.169.236; 6.G.169.237; 6.G.169.238; 6.G.169.239; 6.G.169.154; 6.G.169.157; 6.G.169.166; 6.G.169.169; 6.G.169.172; 6.G.169.175; 6.G.169.240; 6.G.169.244; 6.G.172.228; 6.G.172.229; 6.G.172.230; 6.G.172.231; 6.G.172.236; 6.G.172.237; 6.G.172.238; 6.G.172.239; 6.G.172.154; 6.G.172.157; 6.G.172.166; 6.G.172.169; 6.G.172.172; 6.G.172.175; 6.G.172.240; 6.G.172.244; 6.G.175.228; 6.G.175.229; 6.G.175.230; 6.G.175.231; 6.G.175.236; 6.G.175.237; 6.G.175.238; 6.G.175.239; 6.G.175.154; 6.G.175.157; 6.G.175.166; 6.G.175.169; 6.G.175.172; 6.G.175.175; 6.G.175.240; 6.G.175.244; 6.G.240.228; 6.G.240.229; 6.G.240.230; 6.G.240.231; 6.G.240.236; 6.G.240.237; 6.G.240.238; 6.G.240.239; 6.G.240.154; 6.G.240.157; 6.G.240.166;

6.G.240.169; 6.G.240.172; 6.G.240.175; 6.G.240.240; 6.G.240.244; 6.G.244.228; 6.G.244.229; 6.G.244.230; 6.G.244.231; 6.G.244.236; 6.G.244.237; 6.G.244.238; 6.G.244.239; 6.G.244.154; 6.G.244.157; 6.G.244.166; 6.G.244.169; 6.G.244.172; 6.G.244.175; 6.G.244.240; 6.G.244.244;

Prodrugs of 6.I

6.I.228.228; 6.I.228.229; 6.I.228.230; 6.I.228.231; 6.I.228.236; 6.I.228.237; 6.I.228.238; 6.I.228.239; 6.I.228.154; 6.I.228.157; 6.I.228.166; 6.I.228.169; 6.I.228.172; 6.I.228.175; 6.I.228.240; 6.I.228.244; 6.I.229.228; 6.I.229.229; 6.I.229.230; 6.I.229.231; 6.I.229.236; 6.I.229.237; 6.I.229.238; 6.I.229.239; 6.I.229.154; 6.I.229.157; 6.I.229.166; 6.I.229.169; 6.I.229.172; 6.I.229.175; 6.I.229.240; 6.I.229.244; 6.I.230.228; 6.I.230.229; 6.I.230.230; 6.I.230.231; 6.I.230.236; 6.I.230.237; 6.I.230.238; 6.I.230.239; 6.I.230.154; 6.I.230.157; 6.I.230.166; 6.I.230.169; 6.I.230.172; 6.I.230.175; 6.I.230.240; 6.I.230.244; 6.I.231.228; 6.I.231.229; 6.I.231.230; 6.I.231.231; 6.I.231.236; 6.I.231.237; 6.I.231.238; 6.I.231.239; 6.I.231.154; 6.I.231.157; 6.I.231.166; 6.I.231.169; 6.I.231.172; 6.I.231.175; 6.I.231.240; 6.I.231.244; 6.I.236.228; 6.I.236.229; 6.I.236.230; 6.I.236.231; 6.I.236.236; 6.I.236.237; 6.I.236.238; 6.I.236.239; 6.I.236.154; 6.I.236.157; 6.I.236.166; 6.I.236.169; 6.I.236.172; 6.I.236.175; 6.I.236.240; 6.I.236.244; 6.I.237.228; 6.I.237.229; 6.I.237.230; 6.I.237.231; 6.I.237.236; 6.I.237.237; 6.I.237.238; 6.I.237.239; 6.I.237.154; 6.I.237.157; 6.I.237.166; 6.I.237.169; 6.I.237.172; 6.I.237.175; 6.I.237.240; 6.I.237.244; 6.I.238.228; 6.I.238.229; 6.I.238.230; 6.I.238.231; 6.I.238.236; 6.I.238.237; 6.I.238.238; 6.I.238.239; 6.I.238.154; 6.I.238.157; 6.I.238.166; 6.I.238.169; 6.I.238.172; 6.I.238.175; 6.I.238.240; 6.I.238.244; 6.I.239.228; 6.I.239.229; 6.I.239.230; 6.I.239.231; 6.I.239.236; 6.I.239.237; 6.I.239.238; 6.I.239.239; 6.I.239.154; 6.I.239.157; 6.I.239.166; 6.I.239.169; 6.I.239.172; 6.I.239.175; 6.I.239.240; 6.I.239.244; 6.I.154.228; 6.I.154.229; 6.I.154.230; 6.I.154.231; 6.I.154.236; 6.I.154.237; 6.I.154.238; 6.I.154.239; 6.I.154.154; 6.I.154.157;

6.I.154.166; 6.I.154.169; 6.I.154.172; 6.I.154.175; 6.I.154.240; 6.I.154.244; 6.I.157.228; 6.I.157.229; 6.I.157.230; 6.I.157.231; 6.I.157.236; 6.I.157.237; 6.I.157.238; 6.I.157.239; 6.I.157.154; 6.I.157.157; 6.I.157.166; 6.I.157.169; 6.I.157.172; 6.I.157.175; 6.I.157.240; 6.I.157.244; 6.I.166.228; 6.I.166.229; 6.I.166.230; 6.I.166.231; 6.I.166.236; 6.I.166.237; 6.I.166.238; 6.I.166.239; 6.I.166.154; 6.I.166.157; 6.I.166.166; 6.I.166.169; 6.I.166.172; 6.I.166.175; 6.I.166.240; 6.I.166.244; 6.I.169.228; 6.I.169.229; 6.I.169.230; 6.I.169.231; 6.I.169.236; 6.I.169.237; 6.I.169.238; 6.I.169.239; 6.I.169.154; 6.I.169.157; 6.I.169.166; 6.I.169.169; 6.I.169.172; 6.I.169.175; 6.I.169.240; 6.I.169.244; 6.I.172.228; 6.I.172.229; 6.I.172.230; 6.I.172.231; 6.I.172.236; 6.I.172.237; 6.I.172.238; 6.I.172.239; 6.I.172.154; 6.I.172.157; 6.I.172.166; 6.I.172.169; 6.I.172.172; 6.I.172.175; 6.I.172.240; 6.I.172.244; 6.I.175.228; 6.I.175.229; 6.I.175.230; 6.I.175.231; 6.I.175.236; 6.I.175.237; 6.I.175.238; 6.I.175.239; 6.I.175.154; 6.I.175.157; 6.I.175.166; 6.I.175.169; 6.I.175.172; 6.I.175.175; 6.I.175.240; 6.I.175.244; 6.I.240.228; 6.I.240.229; 6.I.240.230; 6.I.240.231; 6.I.240.236; 6.I.240.237; 6.I.240.238; 6.I.240.239; 6.I.240.154; 6.I.240.157; 6.I.240.166; 6.I.240.169; 6.I.240.172; 6.I.240.175; 6.I.240.240; 6.I.240.244; 6.I.244.228; 6.I.244.229; 6.I.244.230; 6.I.244.231; 6.I.244.236; 6.I.244.237; 6.I.244.238; 6.I.244.239; 6.I.244.154; 6.I.244.157; 6.I.244.166; 6.I.244.169; 6.I.244.172; 6.I.244.175; 6.I.244.240; 6.I.244.244;

Prodrugs of 6.J

6.J.228.228; 6.J.228.229; 6.J.228.230; 6.J.228.231; 6.J.228.236; 6.J.228.237; 6.J.228.238; 6.J.228.239; 6.J.228.154; 6.J.228.157; 6.J.228.166; 6.J.228.169; 6.J.228.172; 6.J.228.175; 6.J.228.240; 6.J.228.244; 6.J.229.228; 6.J.229.229; 6.J.229.230; 6.J.229.231; 6.J.229.236; 6.J.229.237; 6.J.229.238; 6.J.229.239; 6.J.229.154; 6.J.229.157; 6.J.229.166; 6.J.229.169; 6.J.229.172; 6.J.229.175; 6.J.229.240; 6.J.229.244; 6.J.230.228; 6.J.230.229; 6.J.230.230; 6.J.230.231; 6.J.230.236; 6.J.230.237; 6.J.230.238; 6.J.230.239; 6.J.230.154; 6.J.230.157; 6.J.230.166; 6.J.230.169; 6.J.230.172; 6.J.230.175; 6.J.230.240; 6.J.230.244;

6.J.231.228; 6.J.231.229; 6.J.231.230; 6.J.231.231; 6.J.231.236; 6.J.231.237; 6.J.231.238; 6.J.231.239; 6.J.231.154; 6.J.231.157; 6.J.231.166; 6.J.231.169; 6.J.231.172; 6.J.231.175; 6.J.231.240; 6.J.231.244; 6.J.236.228; 6.J.236.229; 6.J.236.230; 6.J.236.231; 6.J.236.236; 6.J.236.237; 6.J.236.238; 6.J.236.239; 6.J.236.154; 6.J.236.157; 6.J.236.166; 6.J.236.169; 6.J.236.172; 6.J.236.175; 6.J.236.240; 6.J.236.244; 6.J.237.228; 6.J.237.229; 6.J.237.230; 6.J.237.231; 6.J.237.236; 6.J.237.237; 6.J.237.238; 6.J.237.239; 6.J.237.154; 6.J.237.157; 6.J.237.166; 6.J.237.169; 6.J.237.172; 6.J.237.175; 6.J.237.240; 6.J.237.244; 6.J.238.228; 6.J.238.229; 6.J.238.230; 6.J.238.231; 6.J.238.236; 6.J.238.237; 6.J.238.238; 6.J.238.239; 6.J.238.154; 6.J.238.157; 6.J.238.166; 6.J.238.169; 6.J.238.172; 6.J.238.175; 6.J.238.240; 6.J.238.244; 6.J.239.228; 6.J.239.229; 6.J.239.230; 6.J.239.231; 6.J.239.236; 6.J.239.237; 6.J.239.238; 6.J.239.239; 6.J.239.154; 6.J.239.157; 6.J.239.166; 6.J.239.169; 6.J.239.172; 6.J.239.175; 6.J.239.240; 6.J.239.244; 6.J.154.228; 6.J.154.229; 6.J.154.230; 6.J.154.231; 6.J.154.236; 6.J.154.237; 6.J.154.238; 6.J.154.239; 6.J.154.154; 6.J.154.157; 6.J.154.166; 6.J.154.169; 6.J.154.172; 6.J.154.175; 6.J.154.240; 6.J.154.244; 6.J.157.228; 6.J.157.229; 6.J.157.230; 6.J.157.231; 6.J.157.236; 6.J.157.237; 6.J.157.238; 6.J.157.239; 6.J.157.154; 6.J.157.157; 6.J.157.166; 6.J.157.169; 6.J.157.172; 6.J.157.175; 6.J.157.240; 6.J.157.244; 6.J.166.228; 6.J.166.229; 6.J.166.230; 6.J.166.231; 6.J.166.236; 6.J.166.237; 6.J.166.238; 6.J.166.239; 6.J.166.154; 6.J.166.157; 6.J.166.166; 6.J.166.169; 6.J.166.172; 6.J.166.175; 6.J.166.240; 6.J.166.244; 6.J.169.228; 6.J.169.229; 6.J.169.230; 6.J.169.231; 6.J.169.236; 6.J.169.237; 6.J.169.238; 6.J.169.239; 6.J.169.154; 6.J.169.157; 6.J.169.166; 6.J.169.169; 6.J.169.172; 6.J.169.175; 6.J.169.240; 6.J.169.244; 6.J.172.228; 6.J.172.229; 6.J.172.230; 6.J.172.231; 6.J.172.236; 6.J.172.237; 6.J.172.238; 6.J.172.239; 6.J.172.154; 6.J.172.157; 6.J.172.166; 6.J.172.169; 6.J.172.172; 6.J.172.175; 6.J.172.240; 6.J.172.244; 6.J.175.228; 6.J.175.229; 6.J.175.230; 6.J.175.231; 6.J.175.236; 6.J.175.237; 6.J.175.238; 6.J.175.239; 6.J.175.154; 6.J.175.157; 6.J.175.166; 6.J.175.169; 6.J.175.172; 6.J.175.175; 6.J.175.240; 6.J.175.244; 6.J.240.228; 6.J.240.229; 6.J.240.230; 6.J.240.231;

6.J.240.236; 6.J.240.237; 6.J.240.238; 6.J.240.239; 6.J.240.154; 6.J.240.157; 6.J.240.166; 6.J.240.169; 6.J.240.172; 6.J.240.175; 6.J.240.240; 6.J.240.244; 6.J.244.228; 6.J.244.229; 6.J.244.230; 6.J.244.231; 6.J.244.236; 6.J.244.237; 6.J.244.238; 6.J.244.239; 6.J.244.154; 6.J.244.157; 6.J.244.166; 6.J.244.169; 6.J.244.172; 6.J.244.175; 6.J.244.240; 6.J.244.244;

Prodrugs of 6.L

6.L.228.228; 6.L.228.229; 6.L.228.230; 6.L.228.231; 6.L.228.236; 6.L.228.237; 6.L.228.238; 6.L.228.239; 6.L.228.154; 6.L.228.157; 6.L.228.166; 6.L.228.169; 6.L.228.172; 6.L.228.175; 6.L.228.240; 6.L.228.244; 6.L.229.228; 6.L.229.229; 6.L.229.230; 6.L.229.231; 6.L.229.236; 6.L.229.237; 6.L.229.238; 6.L.229.239; 6.L.229.154; 6.L.229.157; 6.L.229.166; 6.L.229.169; 6.L.229.172; 6.L.229.175; 6.L.229.240; 6.L.229.244; 6.L.230.228; 6.L.230.229; 6.L.230.230; 6.L.230.231; 6.L.230.236; 6.L.230.237; 6.L.230.238; 6.L.230.239; 6.L.230.154; 6.L.230.157; 6.L.230.166; 6.L.230.169; 6.L.230.172; 6.L.230.175; 6.L.230.240; 6.L.230.244; 6.L.231.228; 6.L.231.229; 6.L.231.230; 6.L.231.231; 6.L.231.236; 6.L.231.237; 6.L.231.238; 6.L.231.239; 6.L.231.154; 6.L.231.157; 6.L.231.166; 6.L.231.169; 6.L.231.172; 6.L.231.175; 6.L.231.240; 6.L.231.244; 6.L.236.228; 6.L.236.229; 6.L.236.230; 6.L.236.231; 6.L.236.236; 6.L.236.237; 6.L.236.238; 6.L.236.239; 6.L.236.154; 6.L.236.157; 6.L.236.166; 6.L.236.169; 6.L.236.172; 6.L.236.175; 6.L.236.240; 6.L.236.244; 6.L.237.228; 6.L.237.229; 6.L.237.230; 6.L.237.231; 6.L.237.236; 6.L.237.237; 6.L.237.238; 6.L.237.239; 6.L.237.154; 6.L.237.157; 6.L.237.166; 6.L.237.169; 6.L.237.172; 6.L.237.175; 6.L.237.240; 6.L.237.244; 6.L.238.228; 6.L.238.229; 6.L.238.230; 6.L.238.231; 6.L.238.236; 6.L.238.237; 6.L.238.238; 6.L.238.239; 6.L.238.154; 6.L.238.157; 6.L.238.166; 6.L.238.169; 6.L.238.172; 6.L.238.175; 6.L.238.240; 6.L.238.244; 6.L.239.228; 6.L.239.229; 6.L.239.230; 6.L.239.231; 6.L.239.236; 6.L.239.237; 6.L.239.238; 6.L.239.239; 6.L.239.154; 6.L.239.157; 6.L.239.166; 6.L.239.169; 6.L.239.172; 6.L.239.175; 6.L.239.240; 6.L.239.244; 6.L.154.228; 6.L.154.229; 6.L.154.230; 6.L.154.231; 6.L.154.236; 6.L.154.237; 6.L.154.238; 6.L.154.239; 6.L.154.154;

6.L.154.157; 6.L.154.166; 6.L.154.169; 6.L.154.172; 6.L.154.175; 6.L.154.240; 6.L.154.244; 6.L.157.228; 6.L.157.229; 6.L.157.230; 6.L.157.231; 6.L.157.236; 6.L.157.237; 6.L.157.238; 6.L.157.239; 6.L.157.154; 6.L.157.157; 6.L.157.166; 6.L.157.169; 6.L.157.172; 6.L.157.175; 6.L.157.240; 6.L.157.244; 6.L.166.228; 6.L.166.229; 6.L.166.230; 6.L.166.231; 6.L.166.236; 6.L.166.237; 6.L.166.238; 6.L.166.239; 6.L.166.154; 6.L.166.157; 6.L.166.166; 6.L.166.169; 6.L.166.172; 6.L.166.175; 6.L.166.240; 6.L.166.244; 6.L.169.228; 6.L.169.229; 6.L.169.230; 6.L.169.231; 6.L.169.236; 6.L.169.237; 6.L.169.238; 6.L.169.239; 6.L.169.154; 6.L.169.157; 6.L.169.166; 6.L.169.169; 6.L.169.172; 6.L.169.175; 6.L.169.240; 6.L.169.244; 6.L.172.228; 6.L.172.229; 6.L.172.230; 6.L.172.231; 6.L.172.236; 6.L.172.237; 6.L.172.238; 6.L.172.239; 6.L.172.154; 6.L.172.157; 6.L.172.166; 6.L.172.169; 6.L.172.172; 6.L.172.175; 6.L.172.240; 6.L.172.244; 6.L.175.228; 6.L.175.229; 6.L.175.230; 6.L.175.231; 6.L.175.236; 6.L.175.237; 6.L.175.238; 6.L.175.239; 6.L.175.154; 6.L.175.157; 6.L.175.166; 6.L.175.169; 6.L.175.172; 6.L.175.175; 6.L.175.240; 6.L.175.244; 6.L.240.228; 6.L.240.229; 6.L.240.230; 6.L.240.231; 6.L.240.236; 6.L.240.237; 6.L.240.238; 6.L.240.239; 6.L.240.154; 6.L.240.157; 6.L.240.166; 6.L.240.169; 6.L.240.172; 6.L.240.175; 6.L.240.240; 6.L.240.244; 6.L.244.228; 6.L.244.229; 6.L.244.230; 6.L.244.231; 6.L.244.236; 6.L.244.237; 6.L.244.238; 6.L.244.239; 6.L.244.154; 6.L.244.157; 6.L.244.166; 6.L.244.169; 6.L.244.172; 6.L.244.175; 6.L.244.240; 6.L.244.244;

Prodrugs of 6.O

6.O.228.228; 6.O.228.229; 6.O.228.230; 6.O.228.231; 6.O.228.236; 6.O.228.237; 6.O.228.238; 6.O.228.239; 6.O.228.154; 6.O.228.157; 6.O.228.166; 6.O.228.169; 6.O.228.172; 6.O.228.175; 6.O.228.240; 6.O.228.244; 6.O.229.228; 6.O.229.229; 6.O.229.230; 6.O.229.231; 6.O.229.236; 6.O.229.237; 6.O.229.238; 6.O.229.239; 6.O.229.154; 6.O.229.157; 6.O.229.166; 6.O.229.169; 6.O.229.172; 6.O.229.175; 6.O.229.240; 6.O.229.244; 6.O.230.228; 6.O.230.229; 6.O.230.230; 6.O.230.231; 6.O.230.236; 6.O.230.237; 6.O.230.238; 6.O.230.239;

6.O.230.154; 6.O.230.157; 6.O.230.166; 6.O.230.169; 6.O.230.172; 6.O.230.175; 6.O.230.240; 6.O.230.244; 6.O.231.228; 6.O.231.229; 6.O.231.230; 6.O.231.231; 6.O.231.236; 6.O.231.237; 6.O.231.238; 6.O.231.239; 6.O.231.154; 6.O.231.157; 6.O.231.166; 6.O.231.169; 6.O.231.172; 6.O.231.175; 6.O.231.240; 6.O.231.244; 6.O.236.228; 6.O.236.229; 6.O.236.230; 6.O.236.231; 6.O.236.236; 6.O.236.237; 6.O.236.238; 6.O.236.239; 6.O.236.154; 6.O.236.157; 6.O.236.166; 6.O.236.169; 6.O.236.172; 6.O.236.175; 6.O.236.240; 6.O.236.244; 6.O.237.228; 6.O.237.229; 6.O.237.230; 6.O.237.231; 6.O.237.236; 6.O.237.237; 6.O.237.238; 6.O.237.239; 6.O.237.154; 6.O.237.157; 6.O.237.166; 6.O.237.169; 6.O.237.172; 6.O.237.175; 6.O.237.240; 6.O.237.244; 6.O.238.228; 6.O.238.229; 6.O.238.230; 6.O.238.231; 6.O.238.236; 6.O.238.237; 6.O.238.238; 6.O.238.239; 6.O.238.154; 6.O.238.157; 6.O.238.166; 6.O.238.169; 6.O.238.172; 6.O.238.175; 6.O.238.240; 6.O.238.244; 6.O.239.228; 6.O.239.229; 6.O.239.230; 6.O.239.231; 6.O.239.236; 6.O.239.237; 6.O.239.238; 6.O.239.239; 6.O.239.154; 6.O.239.157; 6.O.239.166; 6.O.239.169; 6.O.239.172; 6.O.239.175; 6.O.239.240; 6.O.239.244; 6.O.154.228; 6.O.154.229; 6.O.154.230; 6.O.154.231; 6.O.154.236; 6.O.154.237; 6.O.154.238; 6.O.154.239; 6.O.154.154; 6.O.154.157; 6.O.154.166; 6.O.154.169; 6.O.154.172; 6.O.154.175; 6.O.154.240; 6.O.154.244; 6.O.157.228; 6.O.157.229; 6.O.157.230; 6.O.157.231; 6.O.157.236; 6.O.157.237; 6.O.157.238; 6.O.157.239; 6.O.157.154; 6.O.157.157; 6.O.157.166; 6.O.157.169; 6.O.157.172; 6.O.157.175; 6.O.157.240; 6.O.157.244; 6.O.166.228; 6.O.166.229; 6.O.166.230; 6.O.166.231; 6.O.166.236; 6.O.166.237; 6.O.166.238; 6.O.166.239; 6.O.166.154; 6.O.166.157; 6.O.166.166; 6.O.166.169; 6.O.166.172; 6.O.166.175; 6.O.166.240; 6.O.166.244; 6.O.169.228; 6.O.169.229; 6.O.169.230; 6.O.169.231; 6.O.169.236; 6.O.169.237; 6.O.169.238; 6.O.169.239; 6.O.169.154; 6.O.169.157; 6.O.169.166; 6.O.169.169; 6.O.169.172; 6.O.169.175;

6.O.169.240; 6.O.169.244; 6.O.172.228; 6.O.172.229; 6.O.172.230; 6.O.172.231; 6.O.172.236; 6.O.172.237; 6.O.172.238; 6.O.172.239; 6.O.172.154; 6.O.172.157; 6.O.172.166; 6.O.172.169; 6.O.172.172; 6.O.172.175; 6.O.172.240; 6.O.172.244; 6.O.175.228; 6.O.175.229; 6.O.175.230; 6.O.175.231; 6.O.175.236; 6.O.175.237; 6.O.175.238; 6.O.175.239; 6.O.175.154; 6.O.175.157; 6.O.175.166; 6.O.175.169; 6.O.175.172; 6.O.175.175; 6.O.175.240; 6.O.175.244; 6.O.240.228; 6.O.240.229; 6.O.240.230; 6.O.240.231; 6.O.240.236; 6.O.240.237; 6.O.240.238; 6.O.240.239; 6.O.240.154; 6.O.240.157; 6.O.240.166; 6.O.240.169; 6.O.240.172; 6.O.240.175; 6.O.240.240; 6.O.240.244; 6.O.244.228; 6.O.244.229; 6.O.244.230; 6.O.244.231; 6.O.244.236; 6.O.244.237; 6.O.244.238; 6.O.244.239; 6.O.244.154; 6.O.244.157; 6.O.244.166; 6.O.244.169; 6.O.244.172; 6.O.244.175; 6.O.244.240; 6.O.244.244;

Prodrugs of 6.P

6.P.228.228; 6.P.228.229; 6.P.228.230; 6.P.228.231; 6.P.228.236; 6.P.228.237; 6.P.228.238; 6.P.228.239; 6.P.228.154; 6.P.228.157; 6.P.228.166; 6.P.228.169; 6.P.228.172; 6.P.228.175; 6.P.228.240; 6.P.228.244; 6.P.229.228; 6.P.229.229; 6.P.229.230; 6.P.229.231; 6.P.229.236; 6.P.229.237; 6.P.229.238; 6.P.229.239; 6.P.229.154; 6.P.229.157; 6.P.229.166; 6.P.229.169; 6.P.229.172; 6.P.229.175; 6.P.229.240; 6.P.229.244; 6.P.230.228; 6.P.230.229; 6.P.230.230; 6.P.230.231; 6.P.230.236; 6.P.230.237; 6.P.230.238; 6.P.230.239; 6.P.230.154; 6.P.230.157; 6.P.230.166; 6.P.230.169; 6.P.230.172; 6.P.230.175; 6.P.230.240; 6.P.230.244; 6.P.231.228; 6.P.231.229; 6.P.231.230; 6.P.231.231; 6.P.231.236; 6.P.231.237; 6.P.231.238; 6.P.231.239; 6.P.231.154; 6.P.231.157; 6.P.231.166; 6.P.231.169; 6.P.231.172; 6.P.231.175; 6.P.231.240; 6.P.231.244; 6.P.236.228; 6.P.236.229; 6.P.236.230; 6.P.236.231; 6.P.236.236; 6.P.236.237; 6.P.236.238; 6.P.236.239; 6.P.236.154; 6.P.236.157; 6.P.236.166; 6.P.236.169; 6.P.236.172; 6.P.236.175; 6.P.236.240; 6.P.236.244; 6.P.237.228; 6.P.237.229; 6.P.237.230;

6.P.237.231; 6.P.237.236; 6.P.237.237; 6.P.237.238; 6.P.237.239; 6.P.237.154; 6.P.237.157; 6.P.237.166; 6.P.237.169; 6.P.237.172; 6.P.237.175; 6.P.237.240; 6.P.237.244; 6.P.238.228; 6.P.238.229; 6.P.238.230; 6.P.238.231; 6.P.238.236; 6.P.238.237; 6.P.238.238; 6.P.238.239; 6.P.238.154; 6.P.238.157; 6.P.238.166; 6.P.238.169; 6.P.238.172; 6.P.238.175; 6.P.238.240; 6.P.238.244; 6.P.239.228; 6.P.239.229; 6.P.239.230; 6.P.239.231; 6.P.239.236; 6.P.239.237; 6.P.239.238; 6.P.239.239; 6.P.239.154; 6.P.239.157; 6.P.239.166; 6.P.239.169; 6.P.239.172; 6.P.239.175; 6.P.239.240; 6.P.239.244; 6.P.154.228; 6.P.154.229; 6.P.154.230; 6.P.154.231; 6.P.154.236; 6.P.154.237; 6.P.154.238; 6.P.154.239; 6.P.154.154; 6.P.154.157; 6.P.154.166; 6.P.154.169; 6.P.154.172; 6.P.154.175; 6.P.154.240; 6.P.154.244; 6.P.157.228; 6.P.157.229; 6.P.157.230; 6.P.157.231; 6.P.157.236; 6.P.157.237; 6.P.157.238; 6.P.157.239; 6.P.157.154; 6.P.157.157; 6.P.157.166; 6.P.157.169; 6.P.157.172; 6.P.157.175; 6.P.157.240; 6.P.157.244; 6.P.166.228; 6.P.166.229; 6.P.166.230; 6.P.166.231; 6.P.166.236; 6.P.166.237; 6.P.166.238; 6.P.166.239; 6.P.166.154; 6.P.166.157; 6.P.166.166; 6.P.166.169; 6.P.166.172; 6.P.166.175; 6.P.166.240; 6.P.166.244; 6.P.169.228; 6.P.169.229; 6.P.169.230; 6.P.169.231; 6.P.169.236; 6.P.169.237; 6.P.169.238; 6.P.169.239; 6.P.169.154; 6.P.169.157; 6.P.169.166; 6.P.169.169; 6.P.169.172; 6.P.169.175; 6.P.169.240; 6.P.169.244; 6.P.172.228; 6.P.172.229; 6.P.172.230; 6.P.172.231; 6.P.172.236; 6.P.172.237; 6.P.172.238; 6.P.172.239; 6.P.172.154; 6.P.172.157; 6.P.172.166; 6.P.172.169; 6.P.172.172; 6.P.172.175; 6.P.172.240; 6.P.172.244; 6.P.175.228; 6.P.175.229; 6.P.175.230; 6.P.175.231; 6.P.175.236; 6.P.175.237; 6.P.175.238; 6.P.175.239; 6.P.175.154; 6.P.175.157; 6.P.175.166; 6.P.175.169; 6.P.175.172; 6.P.175.175; 6.P.175.240; 6.P.175.244; 6.P.240.228; 6.P.240.229; 6.P.240.230; 6.P.240.231; 6.P.240.236; 6.P.240.237; 6.P.240.238; 6.P.240.239; 6.P.240.154; 6.P.240.157; 6.P.240.166; 6.P.240.169; 6.P.240.172; 6.P.240.175; 6.P.240.240; 6.P.240.244; 6.P.244.228; 6.P.244.229; 6.P.244.230; 6.P.244.231; 6.P.244.236; 6.P.244.237; 6.P.244.238; 6.P.244.239; 6.P.244.154; 6.P.244.157; 6.P.244.166; 6.P.244.169; 6.P.244.172; 6.P.244.175; 6.P.244.240; 6.P.244.244;

Prodrugs of 6.U

6.U.228.228; 6.U.228.229; 6.U.228.230; 6.U.228.231; 6.U.228.236; 6.U.228.237; 6.U.228.238; 6.U.228.239; 6.U.228.154; 6.U.228.157; 6.U.228.166; 6.U.228.169; 6.U.228.172; 6.U.228.175; 6.U.228.240; 6.U.228.244; 6.U.229.228; 6.U.229.229; 6.U.229.230; 6.U.229.231; 6.U.229.236; 6.U.229.237; 6.U.229.238; 6.U.229.239; 6.U.229.154; 6.U.229.157; 6.U.229.166; 6.U.229.169; 6.U.229.172; 6.U.229.175; 6.U.229.240; 6.U.229.244; 6.U.230.228; 6.U.230.229; 6.U.230.230; 6.U.230.231; 6.U.230.236; 6.U.230.237; 6.U.230.238; 6.U.230.239; 6.U.230.154; 6.U.230.157; 6.U.230.166; 6.U.230.169; 6.U.230.172; 6.U.230.175; 6.U.230.240; 6.U.230.244; 6.U.231.228; 6.U.231.229; 6.U.231.230; 6.U.231.231; 6.U.231.236; 6.U.231.237; 6.U.231.238; 6.U.231.239; 6.U.231.154; 6.U.231.157; 6.U.231.166; 6.U.231.169; 6.U.231.172; 6.U.231.175; 6.U.231.240; 6.U.231.244; 6.U.236.228; 6.U.236.229; 6.U.236.230; 6.U.236.231; 6.U.236.236; 6.U.236.237; 6.U.236.238; 6.U.236.239; 6.U.236.154; 6.U.236.157; 6.U.236.166; 6.U.236.169; 6.U.236.172; 6.U.236.175; 6.U.236.240; 6.U.236.244; 6.U.237.228; 6.U.237.229; 6.U.237.230; 6.U.237.231; 6.U.237.236; 6.U.237.237; 6.U.237.238; 6.U.237.239; 6.U.237.154; 6.U.237.157; 6.U.237.166; 6.U.237.169; 6.U.237.172; 6.U.237.175; 6.U.237.240; 6.U.237.244; 6.U.238.228; 6.U.238.229; 6.U.238.230; 6.U.238.231; 6.U.238.236; 6.U.238.237; 6.U.238.238; 6.U.238.239; 6.U.238.154; 6.U.238.157; 6.U.238.166; 6.U.238.169; 6.U.238.172; 6.U.238.175; 6.U.238.240; 6.U.238.244; 6.U.239.228; 6.U.239.229; 6.U.239.230; 6.U.239.231; 6.U.239.236; 6.U.239.237; 6.U.239.238; 6.U.239.239; 6.U.239.154; 6.U.239.157; 6.U.239.166; 6.U.239.169; 6.U.239.172; 6.U.239.175; 6.U.239.240; 6.U.239.244; 6.U.154.228; 6.U.154.229; 6.U.154.230; 6.U.154.231; 6.U.154.236; 6.U.154.237; 6.U.154.238; 6.U.154.239; 6.U.154.154; 6.U.154.157; 6.U.154.166; 6.U.154.169; 6.U.154.172; 6.U.154.175; 6.U.154.240; 6.U.154.244; 6.U.157.228;

6.U.157.229; 6.U.157.230; 6.U.157.231; 6.U.157.236; 6.U.157.237; 6.U.157.238; 6.U.157.239; 6.U.157.154; 6.U.157.157; 6.U.157.166; 6.U.157.169; 6.U.157.172; 6.U.157.175; 6.U.157.240; 6.U.157.244; 6.U.166.228; 6.U.166.229; 6.U.166.230; 6.U.166.231; 6.U.166.236; 6.U.166.237; 6.U.166.238; 6.U.166.239; 6.U.166.154; 6.U.166.157; 6.U.166.166; 6.U.166.169; 6.U.166.172; 6.U.166.175; 6.U.166.240; 6.U.166.244; 6.U.169.228; 6.U.169.229; 6.U.169.230; 6.U.169.231; 6.U.169.236; 6.U.169.237; 6.U.169.238; 6.U.169.239; 6.U.169.154; 6.U.169.157; 6.U.169.166; 6.U.169.169; 6.U.169.172; 6.U.169.175; 6.U.169.240; 6.U.169.244; 6.U.172.228; 6.U.172.229; 6.U.172.230; 6.U.172.231; 6.U.172.236; 6.U.172.237; 6.U.172.238; 6.U.172.239; 6.U.172.154; 6.U.172.157; 6.U.172.166; 6.U.172.169; 6.U.172.172; 6.U.172.175; 6.U.172.240; 6.U.172.244; 6.U.175.228; 6.U.175.229; 6.U.175.230; 6.U.175.231; 6.U.175.236; 6.U.175.237; 6.U.175.238; 6.U.175.239; 6.U.175.154; 6.U.175.157; 6.U.175.166; 6.U.175.169; 6.U.175.172; 6.U.175.175; 6.U.175.240; 6.U.175.244; 6.U.240.228; 6.U.240.229; 6.U.240.230; 6.U.240.231; 6.U.240.236; 6.U.240.237; 6.U.240.238; 6.U.240.239; 6.U.240.154; 6.U.240.157; 6.U.240.166; 6.U.240.169; 6.U.240.172; 6.U.240.175; 6.U.240.240; 6.U.240.244; 6.U.244.228; 6.U.244.229; 6.U.244.230; 6.U.244.231; 6.U.244.236; 6.U.244.237; 6.U.244.238; 6.U.244.239; 6.U.244.154; 6.U.244.157; 6.U.244.166; 6.U.244.169; 6.U.244.172; 6.U.244.175; 6.U.244.240; 6.U.244.244;

Prodrugs of 6.W

6.W.228.228; 6.W.228.229; 6.W.228.230; 6.W.228.231; 6.W.228.236; 6.W.228.237; 6.W.228.238; 6.W.228.239; 6.W.228.154; 6.W.228.157; 6.W.228.166; 6.W.228.169; 6.W.228.172; 6.W.228.175; 6.W.228.240; 6.W.228.244; 6.W.229.228; 6.W.229.229; 6.W.229.230; 6.W.229.231; 6.W.229.236; 6.W.229.237; 6.W.229.238; 6.W.229.239; 6.W.229.154;

6.W.229.157; 6.W.229.166; 6.W.229.169; 6.W.229.172; 6.W.229.175; 6.W.229.240; 6.W.229.244; 6.W.230.228; 6.W.230.229; 6.W.230.230; 6.W.230.231; 6.W.230.236; 6.W.230.237; 6.W.230.238; 6.W.230.239; 6.W.230.154; 6.W.230.157; 6.W.230.166; 6.W.230.169; 6.W.230.172; 6.W.230.175; 6.W.230.240; 6.W.230.244; 6.W.231.228; 6.W.231.229; 6.W.231.230; 6.W.231.231; 6.W.231.236; 6.W.231.237; 6.W.231.238; 6.W.231.239; 6.W.231.154; 6.W.231.157; 6.W.231.166; 6.W.231.169; 6.W.231.172; 6.W.231.175; 6.W.231.240; 6.W.231.244; 6.W.236.228; 6.W.236.229; 6.W.236.230; 6.W.236.231; 6.W.236.236; 6.W.236.237; 6.W.236.238; 6.W.236.239; 6.W.236.154; 6.W.236.157; 6.W.236.166; 6.W.236.169; 6.W.236.172; 6.W.236.175; 6.W.236.240; 6.W.236.244; 6.W.237.228; 6.W.237.229; 6.W.237.230; 6.W.237.231; 6.W.237.236; 6.W.237.237; 6.W.237.238; 6.W.237.239; 6.W.237.154; 6.W.237.157; 6.W.237.166; 6.W.237.169; 6.W.237.172; 6.W.237.175; 6.W.237.240; 6.W.237.244; 6.W.238.228; 6.W.238.229; 6.W.238.230; 6.W.238.231; 6.W.238.236; 6.W.238.237; 6.W.238.238; 6.W.238.239; 6.W.238.154; 6.W.238.157; 6.W.238.166; 6.W.238.169; 6.W.238.172; 6.W.238.175; 6.W.238.240; 6.W.238.244; 6.W.239.228; 6.W.239.229; 6.W.239.230; 6.W.239.231; 6.W.239.236; 6.W.239.237; 6.W.239.238; 6.W.239.239; 6.W.239.154; 6.W.239.157; 6.W.239.166; 6.W.239.169; 6.W.239.172; 6.W.239.175; 6.W.239.240; 6.W.239.244; 6.W.154.228; 6.W.154.229; 6.W.154.230; 6.W.154.231; 6.W.154.236; 6.W.154.237; 6.W.154.238; 6.W.154.239; 6.W.154.154; 6.W.154.157; 6.W.154.166; 6.W.154.169; 6.W.154.172; 6.W.154.175; 6.W.154.240; 6.W.154.244; 6.W.157.228; 6.W.157.229; 6.W.157.230; 6.W.157.231; 6.W.157.236; 6.W.157.237; 6.W.157.238; 6.W.157.239; 6.W.157.154; 6.W.157.157; 6.W.157.166; 6.W.157.169; 6.W.157.172; 6.W.157.175; 6.W.157.240; 6.W.157.244; 6.W.166.228; 6.W.166.229; 6.W.166.230; 6.W.166.231; 6.W.166.236; 6.W.166.237; 6.W.166.238; 6.W.166.239; 6.W.166.154; 6.W.166.157; 6.W.166.166; 6.W.166.169; 6.W.166.172; 6.W.166.175; 6.W.166.240;

6.W.166.244; 6.W.169.228; 6.W.169.229; 6.W.169.230; 6.W.169.231; 6.W.169.236; 6.W.169.237; 6.W.169.238; 6.W.169.239; 6.W.169.154; 6.W.169.157; 6.W.169.166; 6.W.169.169; 6.W.169.172; 6.W.169.175; 6.W.169.240; 6.W.169.244; 6.W.172.228; 6.W.172.229; 6.W.172.230; 6.W.172.231; 6.W.172.236; 6.W.172.237; 6.W.172.238; 6.W.172.239; 6.W.172.154; 6.W.172.157; 6.W.172.166; 6.W.172.169; 6.W.172.172; 6.W.172.175; 6.W.172.240; 6.W.172.244; 6.W.175.228; 6.W.175.229; 6.W.175.230; 6.W.175.231; 6.W.175.236; 6.W.175.237; 6.W.175.238; 6.W.175.239; 6.W.175.154; 6.W.175.157; 6.W.175.166; 6.W.175.169; 6.W.175.172; 6.W.175.175; 6.W.175.240; 6.W.175.244; 6.W.240.228; 6.W.240.229; 6.W.240.230; 6.W.240.231; 6.W.240.236; 6.W.240.237; 6.W.240.238; 6.W.240.239; 6.W.240.154; 6.W.240.157; 6.W.240.166; 6.W.240.169; 6.W.240.172; 6.W.240.175; 6.W.240.240; 6.W.240.244; 6.W.244.228; 6.W.244.229; 6.W.244.230; 6.W.244.231; 6.W.244.236; 6.W.244.237; 6.W.244.238; 6.W.244.239; 6.W.244.154; 6.W.244.157; 6.W.244.166; 6.W.244.169; 6.W.244.172; 6.W.244.175; 6.W.244.240; 6.W.244.244;

Prodrugs of 6.Y

6.Y.228.228; 6.Y.228.229; 6.Y.228.230; 6.Y.228.231; 6.Y.228.236; 6.Y.228.237; 6.Y.228.238; 6.Y.228.239; 6.Y.228.154; 6.Y.228.157; 6.Y.228.166; 6.Y.228.169; 6.Y.228.172; 6.Y.228.175; 6.Y.228.240; 6.Y.228.244; 6.Y.229.228; 6.Y.229.229; 6.Y.229.230; 6.Y.229.231; 6.Y.229.236; 6.Y.229.237; 6.Y.229.238; 6.Y.229.239; 6.Y.229.154; 6.Y.229.157; 6.Y.229.166; 6.Y.229.169; 6.Y.229.172; 6.Y.229.175; 6.Y.229.240; 6.Y.229.244; 6.Y.230.228; 6.Y.230.229; 6.Y.230.230; 6.Y.230.231; 6.Y.230.236; 6.Y.230.237; 6.Y.230.238; 6.Y.230.239; 6.Y.230.154; 6.Y.230.157; 6.Y.230.166; 6.Y.230.169; 6.Y.230.172; 6.Y.230.175; 6.Y.230.240; 6.Y.230.244; 6.Y.231.228; 6.Y.231.229; 6.Y.231.230; 6.Y.231.231; 6.Y.231.236; 6.Y.231.237; 6.Y.231.238; 6.Y.231.239; 6.Y.231.154; 6.Y.231.157; 6.Y.231.166; 6.Y.231.169;

6.Y.231.172; 6.Y.231.175; 6.Y.231.240; 6.Y.231.244; 6.Y.236.228; 6.Y.236.229; 6.Y.236.230; 6.Y.236.231; 6.Y.236.236; 6.Y.236.237; 6.Y.236.238; 6.Y.236.239; 6.Y.236.154; 6.Y.236.157; 6.Y.236.166; 6.Y.236.169; 6.Y.236.172; 6.Y.236.175; 6.Y.236.240; 6.Y.236.244; 6.Y.237.228; 6.Y.237.229; 6.Y.237.230; 6.Y.237.231; 6.Y.237.236; 6.Y.237.237; 6.Y.237.238; 6.Y.237.239; 6.Y.237.154; 6.Y.237.157; 6.Y.237.166; 6.Y.237.169; 6.Y.237.172; 6.Y.237.175; 6.Y.237.240; 6.Y.237.244; 6.Y.238.228; 6.Y.238.229; 6.Y.238.230; 6.Y.238.231; 6.Y.238.236; 6.Y.238.237; 6.Y.238.238; 6.Y.238.239; 6.Y.238.154; 6.Y.238.157; 6.Y.238.166; 6.Y.238.169; 6.Y.238.172; 6.Y.238.175; 6.Y.238.240; 6.Y.238.244; 6.Y.239.228; 6.Y.239.229; 6.Y.239.230; 6.Y.239.231; 6.Y.239.236; 6.Y.239.237; 6.Y.239.238; 6.Y.239.239; 6.Y.239.154; 6.Y.239.157; 6.Y.239.166; 6.Y.239.169; 6.Y.239.172; 6.Y.239.175; 6.Y.239.240; 6.Y.239.244; 6.Y.154.228; 6.Y.154.229; 6.Y.154.230; 6.Y.154.231; 6.Y.154.236; 6.Y.154.237; 6.Y.154.238; 6.Y.154.239; 6.Y.154.154; 6.Y.154.157; 6.Y.154.166; 6.Y.154.169; 6.Y.154.172; 6.Y.154.175; 6.Y.154.240; 6.Y.154.244; 6.Y.157.228; 6.Y.157.229; 6.Y.157.230; 6.Y.157.231; 6.Y.157.236; 6.Y.157.237; 6.Y.157.238; 6.Y.157.239; 6.Y.157.154; 6.Y.157.157; 6.Y.157.166; 6.Y.157.169; 6.Y.157.172; 6.Y.157.175; 6.Y.157.240; 6.Y.157.244; 6.Y.166.228; 6.Y.166.229; 6.Y.166.230; 6.Y.166.231; 6.Y.166.236; 6.Y.166.237; 6.Y.166.238; 6.Y.166.239; 6.Y.166.154; 6.Y.166.157; 6.Y.166.166; 6.Y.166.169; 6.Y.166.172; 6.Y.166.175; 6.Y.166.240; 6.Y.166.244; 6.Y.169.228; 6.Y.169.229; 6.Y.169.230; 6.Y.169.231; 6.Y.169.236; 6.Y.169.237; 6.Y.169.238; 6.Y.169.239; 6.Y.169.154; 6.Y.169.157; 6.Y.169.166; 6.Y.169.169; 6.Y.169.172; 6.Y.169.175; 6.Y.169.240; 6.Y.169.244; 6.Y.172.228; 6.Y.172.229; 6.Y.172.230; 6.Y.172.231; 6.Y.172.236; 6.Y.172.237; 6.Y.172.238; 6.Y.172.239; 6.Y.172.154; 6.Y.172.157; 6.Y.172.166; 6.Y.172.169; 6.Y.172.172; 6.Y.172.175; 6.Y.172.240; 6.Y.172.244; 6.Y.175.228; 6.Y.175.229; 6.Y.175.230; 6.Y.175.231; 6.Y.175.236; 6.Y.175.237; 6.Y.175.238; 6.Y.175.239; 6.Y.175.154; 6.Y.175.157; 6.Y.175.166; 6.Y.175.169;

6.Y.175.172; 6.Y.175.175; 6.Y.175.240; 6.Y.175.244; 6.Y.240.228; 6.Y.240.229; 6.Y.240.230; 6.Y.240.231; 6.Y.240.236; 6.Y.240.237; 6.Y.240.238; 6.Y.240.239; 6.Y.240.154; 6.Y.240.157; 6.Y.240.166; 6.Y.240.169; 6.Y.240.172; 6.Y.240.175; 6.Y.240.240; 6.Y.240.244; 6.Y.244.228; 6.Y.244.229; 6.Y.244.230; 6.Y.244.231; 6.Y.244.236; 6.Y.244.237; 6.Y.244.238; 6.Y.244.239; 6.Y.244.154; 6.Y.244.157; 6.Y.244.166; 6.Y.244.169; 6.Y.244.172; 6.Y.244.175; 6.Y.244.240; 6.Y.244.244;

Prodrugs of 7.AH

7.AH.4.157; 7.AH.4.158; 7.AH.4.196; 7.AH.4.223; 7.AH.4.240; 7.AH.4.244; 7.AH.4.243; 7.AH.4.247; 7.AH.5.157; 7.AH.5.158; 7.AH.5.196; 7.AH.5.223; 7.AH.5.240; 7.AH.5.244; 7.AH.5.243; 7.AH.5.247; 7.AH.7.157; 7.AH.7.158; 7.AH.7.196; 7.AH.7.223; 7.AH.7.240; 7.AH.7.244; 7.AH.7.243; 7.AH.7.247; 7.AH.15.157; 7.AH.15.158; 7.AH.15.196; 7.AH.15.223; 7.AH.15.240; 7.AH.15.244; 7.AH.15.243; 7.AH.15.247; 7.AH.16.157; 7.AH.16.158; 7.AH.16.196; 7.AH.16.223; 7.AH.16.240; 7.AH.16.244; 7.AH.16.243; 7.AH.16.247; 7.AH.18.157; 7.AH.18.158; 7.AH.18.196; 7.AH.18.223; 7.AH.18.240; 7.AH.18.244; 7.AH.18.243; 7.AH.18.247; 7.AH.26.157; 7.AH.26.158; 7.AH.26.196; 7.AH.26.223; 7.AH.26.240; 7.AH.26.244; 7.AH.26.243; 7.AH.26.247; 7.AH.27.157; 7.AH.27.158; 7.AH.27.196; 7.AH.27.223; 7.AH.27.240; 7.AH.27.244; 7.AH.27.243; 7.AH.27.247; 7.AH.29.157; 7.AH.29.158; 7.AH.29.196; 7.AH.29.223; 7.AH.29.240; 7.AH.29.244; 7.AH.29.243; 7.AH.29.247; 7.AH.54.157; 7.AH.54.158; 7.AH.54.196; 7.AH.54.223; 7.AH.54.240; 7.AH.54.244; 7.AH.54.243; 7.AH.54.247; 7.AH.55.157; 7.AH.55.158; 7.AH.55.196; 7.AH.55.223; 7.AH.55.240; 7.AH.55.244; 7.AH.55.243; 7.AH.55.247; 7.AH.56.157; 7.AH.56.158; 7.AH.56.196; 7.AH.56.223; 7.AH.56.240; 7.AH.56.244; 7.AH.56.243; 7.AH.56.247; 7.AH.157.157; 7.AH.157.158; 7.AH.157.196; 7.AH.157.223; 7.AH.157.240; 7.AH.157.244; 7.AH.157.243; 7.AH.157.247; 7.AH.196.157; 7.AH.196.158; 7.AH.196.196; 7.AH.196.223; 7.AH.196.240; 7.AH.196.244; 7.AH.196.243; 7.AH.196.247; 7.AH.223.157; 7.AH.223.158;

7.AH.223.196; 7.AH.223.223; 7.AH.223.240; 7.AH.223.244; 7.AH.223.243; 7.AH.223.247; 7.AH.240.157; 7.AH.240.158; 7.AH.240.196; 7.AH.240.223; 7.AH.240.240; 7.AH.240.244; 7.AH.240.243; 7.AH.240.247; 7.AH.244.157; 7.AH.244.158; 7.AH.244.196; 7.AH.244.223; 7.AH.244.240; 7.AH.244.244; 7.AH.244.243; 7.AH.244.247; 7.AH.247.157; 7.AH.247.158; 7.AH.247.196; 7.AH.247.223; 7.AH.247.240; 7.AH.247.244; 7.AH.247.243; 7.AH.247.247;

Prodrugs of 7.AJ

7.AJ.4.157; 7.AJ.4.158; 7.AJ.4.196; 7.AJ.4.223; 7.AJ.4.240; 7.AJ.4.244; 7.AJ.4.243; 7.AJ.4.247; 7.AJ.5.157; 7.AJ.5.158; 7.AJ.5.196; 7.AJ.5.223; 7.AJ.5.240; 7.AJ.5.244; 7.AJ.5.243; 7.AJ.5.247; 7.AJ.7.157; 7.AJ.7.158; 7.AJ.7.196; 7.AJ.7.223; 7.AJ.7.240; 7.AJ.7.244; 7.AJ.7.243; 7.AJ.7.247; 7.AJ.15.157; 7.AJ.15.158; 7.AJ.15.196; 7.AJ.15.223; 7.AJ.15.240; 7.AJ.15.244; 7.AJ.15.243; 7.AJ.15.247; 7.AJ.16.157; 7.AJ.16.158; 7.AJ.16.196; 7.AJ.16.223; 7.AJ.16.240; 7.AJ.16.244; 7.AJ.16.243; 7.AJ.16.247; 7.AJ.18.157; 7.AJ.18.158; 7.AJ.18.196; 7.AJ.18.223; 7.AJ.18.240; 7.AJ.18.244; 7.AJ.18.243; 7.AJ.18.247; 7.AJ.26.157; 7.AJ.26.158; 7.AJ.26.196; 7.AJ.26.223; 7.AJ.26.240; 7.AJ.26.244; 7.AJ.26.243; 7.AJ.26.247; 7.AJ.27.157; 7.AJ.27.158; 7.AJ.27.196; 7.AJ.27.223; 7.AJ.27.240; 7.AJ.27.244; 7.AJ.27.243; 7.AJ.27.247; 7.AJ.29.157; 7.AJ.29.158; 7.AJ.29.196; 7.AJ.29.223; 7.AJ.29.240; 7.AJ.29.244; 7.AJ.29.243; 7.AJ.29.247; 7.AJ.54.157; 7.AJ.54.158; 7.AJ.54.196; 7.AJ.54.223; 7.AJ.54.240; 7.AJ.54.244; 7.AJ.54.243; 7.AJ.54.247; 7.AJ.55.157; 7.AJ.55.158; 7.AJ.55.196; 7.AJ.55.223; 7.AJ.55.240; 7.AJ.55.244; 7.AJ.55.243; 7.AJ.55.247; 7.AJ.56.157; 7.AJ.56.158; 7.AJ.56.196; 7.AJ.56.223; 7.AJ.56.240; 7.AJ.56.244; 7.AJ.56.243; 7.AJ.56.247; 7.AJ.157.157; 7.AJ.157.158; 7.AJ.157.196; 7.AJ.157.223; 7.AJ.157.240; 7.AJ.157.244; 7.AJ.157.243; 7.AJ.157.247; 7.AJ.196.157; 7.AJ.196.158; 7.AJ.196.196; 7.AJ.196.223; 7.AJ.196.240; 7.AJ.196.244; 7.AJ.196.243; 7.AJ.196.247; 7.AJ.223.157; 7.AJ.223.158; 7.AJ.223.196; 7.AJ.223.223; 7.AJ.223.240; 7.AJ.223.244; 7.AJ.223.243; 7.AJ.223.247; 7.AJ.240.157; 7.AJ.240.158; 7.AJ.240.196; 7.AJ.240.223; 7.AJ.240.240; 7.AJ.240.244; 7.AJ.240.243; 7.AJ.240.247; 7.AJ.244.157; 7.AJ.244.158; 7.AJ.244.196; 7.AJ.244.223; 7.AJ.244.240; 7.AJ.244.244; 7.AJ.244.243; 7.AJ.244.247;

7.AJ.247.157; 7.AJ.247.158; 7.AJ.247.196; 7.AJ.247.223; 7.AJ.247.240; 7.AJ.247.244; 7.AJ.247.243; 7.AJ.247.247;

Prodrugs of 7.AN

7.AN.4.157; 7.AN.4.158; 7.AN.4.196; 7.AN.4.223; 7.AN.4.240; 7.AN.4.244; 7.AN.4.243; 7.AN.4.247; 7.AN.5.157; 7.AN.5.158; 7.AN.5.196; 7.AN.5.223; 7.AN.5.240; 7.AN.5.244; 7.AN.5.243; 7.AN.5.247; 7.AN.7.157; 7.AN.7.158; 7.AN.7.196; 7.AN.7.223; 7.AN.7.240; 7.AN.7.244; 7.AN.7.243; 7.AN.7.247; 7.AN.15.157; 7.AN.15.158; 7.AN.15.196; 7.AN.15.223; 7.AN.15.240; 7.AN.15.244; 7.AN.15.243; 7.AN.15.247; 7.AN.16.157; 7.AN.16.158; 7.AN.16.196; 7.AN.16.223; 7.AN.16.240; 7.AN.16.244; 7.AN.16.243; 7.AN.16.247; 7.AN.18.157; 7.AN.18.158; 7.AN.18.196; 7.AN.18.223; 7.AN.18.240; 7.AN.18.244; 7.AN.18.243; 7.AN.18.247; 7.AN.26.157; 7.AN.26.158; 7.AN.26.196; 7.AN.26.223; 7.AN.26.240; 7.AN.26.244; 7.AN.26.243; 7.AN.26.247; 7.AN.27.157; 7.AN.27.158; 7.AN.27.196; 7.AN.27.223; 7.AN.27.240; 7.AN.27.244; 7.AN.27.243; 7.AN.27.247; 7.AN.29.157; 7.AN.29.158; 7.AN.29.196; 7.AN.29.223; 7.AN.29.240; 7.AN.29.244; 7.AN.29.243; 7.AN.29.247; 7.AN.54.157; 7.AN.54.158; 7.AN.54.196; 7.AN.54.223; 7.AN.54.240; 7.AN.54.244; 7.AN.54.243; 7.AN.54.247; 7.AN.55.157; 7.AN.55.158; 7.AN.55.196; 7.AN.55.223; 7.AN.55.240; 7.AN.55.244; 7.AN.55.243; 7.AN.55.247; 7.AN.56.157; 7.AN.56.158; 7.AN.56.196; 7.AN.56.223; 7.AN.56.240; 7.AN.56.244; 7.AN.56.243; 7.AN.56.247; 7.AN.157.157; 7.AN.157.158; 7.AN.157.196; 7.AN.157.223; 7.AN.157.240; 7.AN.157.244; 7.AN.157.243; 7.AN.157.247; 7.AN.196.157; 7.AN.196.158; 7.AN.196.196; 7.AN.196.223; 7.AN.196.240; 7.AN.196.244; 7.AN.196.243; 7.AN.196.247; 7.AN.223.157; 7.AN.223.158; 7.AN.223.196; 7.AN.223.223; 7.AN.223.240; 7.AN.223.244; 7.AN.223.243; 7.AN.223.247; 7.AN.240.157; 7.AN.240.158; 7.AN.240.196; 7.AN.240.223; 7.AN.240.240; 7.AN.240.244; 7.AN.240.243; 7.AN.240.247; 7.AN.244.157; 7.AN.244.158; 7.AN.244.196; 7.AN.244.223; 7.AN.244.240; 7.AN.244.244; 7.AN.244.243; 7.AN.244.247; 7.AN.247.157; 7.AN.247.158; 7.AN.247.196; 7.AN.247.223; 7.AN.247.240; 7.AN.247.244; 7.AN.247.243; 7.AN.247.247;

Prodrugs of 7.AP

7.AP.4.157; 7.AP.4.158; 7.AP.4.196; 7.AP.4.223; 7.AP.4.240; 7.AP.4.244; 7.AP.4.243; 7.AP.4.247; 7.AP.5.157; 7.AP.5.158; 7.AP.5.196; 7.AP.5.223; 7.AP.5.240; 7.AP.5.244; 7.AP.5.243; 7.AP.5.247; 7.AP.7.157; 7.AP.7.158; 7.AP.7.196; 7.AP.7.223; 7.AP.7.240; 7.AP.7.244; 7.AP.7.243; 7.AP.7.247; 7.AP.15.157; 7.AP.15.158; 7.AP.15.196; 7.AP.15.223; 7.AP.15.240; 7.AP.15.244; 7.AP.15.243; 7.AP.15.247; 7.AP.16.157; 7.AP.16.158; 7.AP.16.196; 7.AP.16.223; 7.AP.16.240; 7.AP.16.244; 7.AP.16.243; 7.AP.16.247; 7.AP.18.157; 7.AP.18.158; 7.AP.18.196; 7.AP.18.223; 7.AP.18.240; 7.AP.18.244; 7.AP.18.243; 7.AP.18.247; 7.AP.26.157; 7.AP.26.158; 7.AP.26.196; 7.AP.26.223; 7.AP.26.240; 7.AP.26.244; 7.AP.26.243; 7.AP.26.247; 7.AP.27.157; 7.AP.27.158; 7.AP.27.196; 7.AP.27.223; 7.AP.27.240; 7.AP.27.244; 7.AP.27.243; 7.AP.27.247; 7.AP.29.157; 7.AP.29.158; 7.AP.29.196; 7.AP.29.223; 7.AP.29.240; 7.AP.29.244; 7.AP.29.243; 7.AP.29.247; 7.AP.54.157; 7.AP.54.158; 7.AP.54.196; 7.AP.54.223; 7.AP.54.240; 7.AP.54.244; 7.AP.54.243; 7.AP.54.247; 7.AP.55.157; 7.AP.55.158; 7.AP.55.196; 7.AP.55.223; 7.AP.55.240; 7.AP.55.244; 7.AP.55.243; 7.AP.55.247; 7.AP.56.157; 7.AP.56.158; 7.AP.56.196; 7.AP.56.223; 7.AP.56.240; 7.AP.56.244; 7.AP.56.243; 7.AP.56.247; 7.AP.157.157; 7.AP.157.158; 7.AP.157.196; 7.AP.157.223; 7.AP.157.240; 7.AP.157.244; 7.AP.157.243; 7.AP.157.247; 7.AP.196.157; 7.AP.196.158; 7.AP.196.196; 7.AP.196.223; 7.AP.196.240; 7.AP.196.244; 7.AP.196.243; 7.AP.196.247; 7.AP.223.157; 7.AP.223.158; 7.AP.223.196; 7.AP.223.223; 7.AP.223.240; 7.AP.223.244; 7.AP.223.243; 7.AP.223.247; 7.AP.240.157; 7.AP.240.158; 7.AP.240.196; 7.AP.240.223; 7.AP.240.240; 7.AP.240.244; 7.AP.240.243; 7.AP.240.247; 7.AP.244.157; 7.AP.244.158; 7.AP.244.196; 7.AP.244.223; 7.AP.244.240; 7.AP.244.244; 7.AP.244.243; 7.AP.244.247; 7.AP.247.157; 7.AP.247.158; 7.AP.247.196; 7.AP.247.223; 7.AP.247.240; 7.AP.247.244; 7.AP.247.243; 7.AP.247.247;

Prodrugs of 7.AZ

7.AZ.4.157; 7.AZ.4.158; 7.AZ.4.196; 7.AZ.4.223; 7.AZ.4.240; 7.AZ.4.244; 7.AZ.4.243; 7.AZ.4.247; 7.AZ.5.157; 7.AZ.5.158; 7.AZ.5.196; 7.AZ.5.223; 7.AZ.5.240; 7.AZ.5.244; 7.AZ.5.243; 7.AZ.5.247; 7.AZ.7.157; 7.AZ.7.158; 7.AZ.7.196; 7.AZ.7.223; 7.AZ.7.240; 7.AZ.7.244; 7.AZ.7.243; 7.AZ.7.247; 7.AZ.15.157; 7.AZ.15.158; 7.AZ.15.196; 7.AZ.15.223; 7.AZ.15.240; 7.AZ.15.244; 7.AZ.15.243; 7.AZ.15.247; 7.AZ.16.157; 7.AZ.16.158; 7.AZ.16.196; 7.AZ.16.223; 7.AZ.16.240; 7.AZ.16.244; 7.AZ.16.243; 7.AZ.16.247; 7.AZ.18.157; 7.AZ.18.158; 7.AZ.18.196; 7.AZ.18.223; 7.AZ.18.240; 7.AZ.18.244; 7.AZ.18.243; 7.AZ.18.247; 7.AZ.26.157; 7.AZ.26.158; 7.AZ.26.196; 7.AZ.26.223; 7.AZ.26.240; 7.AZ.26.244; 7.AZ.26.243; 7.AZ.26.247; 7.AZ.27.157; 7.AZ.27.158; 7.AZ.27.196; 7.AZ.27.223; 7.AZ.27.240; 7.AZ.27.244; 7.AZ.27.243; 7.AZ.27.247; 7.AZ.29.157; 7.AZ.29.158; 7.AZ.29.196; 7.AZ.29.223; 7.AZ.29.240; 7.AZ.29.244; 7.AZ.29.243; 7.AZ.29.247; 7.AZ.54.157; 7.AZ.54.158; 7.AZ.54.196; 7.AZ.54.223; 7.AZ.54.240; 7.AZ.54.244; 7.AZ.54.243; 7.AZ.54.247; 7.AZ.55.157; 7.AZ.55.158; 7.AZ.55.196; 7.AZ.55.223; 7.AZ.55.240; 7.AZ.55.244; 7.AZ.55.243; 7.AZ.55.247; 7.AZ.56.157; 7.AZ.56.158; 7.AZ.56.196; 7.AZ.56.223; 7.AZ.56.240; 7.AZ.56.244; 7.AZ.56.243; 7.AZ.56.247; 7.AZ.157.157; 7.AZ.157.158; 7.AZ.157.196; 7.AZ.157.223; 7.AZ.157.240; 7.AZ.157.244; 7.AZ.157.243; 7.AZ.157.247; 7.AZ.196.157; 7.AZ.196.158; 7.AZ.196.196; 7.AZ.196.223; 7.AZ.196.240; 7.AZ.196.244; 7.AZ.196.243; 7.AZ.196.247; 7.AZ.223.157; 7.AZ.223.158; 7.AZ.223.196; 7.AZ.223.223; 7.AZ.223.240; 7.AZ.223.244; 7.AZ.223.243; 7.AZ.223.247; 7.AZ.240.157; 7.AZ.240.158; 7.AZ.240.196; 7.AZ.240.223; 7.AZ.240.240; 7.AZ.240.244; 7.AZ.240.243; 7.AZ.240.247; 7.AZ.244.157; 7.AZ.244.158; 7.AZ.244.196; 7.AZ.244.223; 7.AZ.244.240; 7.AZ.244.244; 7.AZ.244.243; 7.AZ.244.247; 7.AZ.247.157; 7.AZ.247.158; 7.AZ.247.196; 7.AZ.247.223; 7.AZ.247.240; 7.AZ.247.244; 7.AZ.247.243; 7.AZ.247.247;

Prodrugs of 7.BF

7.BF.4.157; 7.BF.4.158; 7.BF.4.196; 7.BF.4.223; 7.BF.4.240; 7.BF.4.244; 7.BF.4.243; 7.BF.4.247; 7.BF.5.157; 7.BF.5.158; 7.BF.5.196; 7.BF.5.223;

7.BF.5.240; 7.BF.5.244; 7.BF.5.243; 7.BF.5.247; 7.BF.7.157; 7.BF.7.158; 7.BF.7.196; 7.BF.7.223; 7.BF.7.240; 7.BF.7.244; 7.BF.7.243; 7.BF.7.247; 7.BF.15.157; 7.BF.15.158; 7.BF.15.196; 7.BF.15.223; 7.BF.15.240; 7.BF.15.244; 7.BF.15.243; 7.BF.15.247; 7.BF.16.157; 7.BF.16.158; 7.BF.16.196; 7.BF.16.223; 7.BF.16.240; 7.BF.16.244; 7.BF.16.243; 7.BF.16.247; 7.BF.18.157; 7.BF.18.158; 7.BF.18.196; 7.BF.18.223; 7.BF.18.240; 7.BF.18.244; 7.BF.18.243; 7.BF.18.247; 7.BF.26.157; 7.BF.26.158; 7.BF.26.196; 7.BF.26.223; 7.BF.26.240; 7.BF.26.244; 7.BF.26.243; 7.BF.26.247; 7.BF.27.157; 7.BF.27.158; 7.BF.27.196; 7.BF.27.223; 7.BF.27.240; 7.BF.27.244; 7.BF.27.243; 7.BF.27.247; 7.BF.29.157; 7.BF.29.158; 7.BF.29.196; 7.BF.29.223; 7.BF.29.240; 7.BF.29.244; 7.BF.29.243; 7.BF.29.247; 7.BF.54.157; 7.BF.54.158; 7.BF.54.196; 7.BF.54.223; 7.BF.54.240; 7.BF.54.244; 7.BF.54.243; 7.BF.54.247; 7.BF.55.157; 7.BF.55.158; 7.BF.55.196; 7.BF.55.223; 7.BF.55.240; 7.BF.55.244; 7.BF.55.243; 7.BF.55.247; 7.BF.56.157; 7.BF.56.158; 7.BF.56.196; 7.BF.56.223; 7.BF.56.240; 7.BF.56.244; 7.BF.56.243; 7.BF.56.247; 7.BF.157.157; 7.BF.157.158; 7.BF.157.196; 7.BF.157.223; 7.BF.157.240; 7.BF.157.244; 7.BF.157.243; 7.BF.157.247; 7.BF.196.157; 7.BF.196.158; 7.BF.196.196; 7.BF.196.223; 7.BF.196.240; 7.BF.196.244; 7.BF.196.243; 7.BF.196.247; 7.BF.223.157; 7.BF.223.158; 7.BF.223.196; 7.BF.223.223; 7.BF.223.240; 7.BF.223.244; 7.BF.223.243; 7.BF.223.247; 7.BF.240.157; 7.BF.240.158; 7.BF.240.196; 7.BF.240.223; 7.BF.240.240; 7.BF.240.244; 7.BF.240.243; 7.BF.240.247; 7.BF.244.157; 7.BF.244.158; 7.BF.244.196; 7.BF.244.223; 7.BF.244.240; 7.BF.244.244; 7.BF.244.243; 7.BF.244.247; 7.BF.247.157; 7.BF.247.158; 7.BF.247.196; 7.BF.247.223; 7.BF.247.240; 7.BF.247.244; 7.BF.247.243; 7.BF.247.247;

Prodrugs of 7.CI

7.CI.4.157; 7.CI.4.158; 7.CI.4.196; 7.CI.4.223; 7.CI.4.240; 7.CI.4.244; 7.CI.4.243; 7.CI.4.247; 7.CI.5.157; 7.CI.5.158; 7.CI.5.196; 7.CI.5.223; 7.CI.5.240; 7.CI.5.244; 7.CI.5.243; 7.CI.5.247; 7.CI.7.157; 7.CI.7.158; 7.CI.7.196; 7.CI.7.223; 7.CI.7.240; 7.CI.7.244; 7.CI.7.243; 7.CI.7.247;

7.CI.15.157; 7.CI.15.158; 7.CI.15.196; 7.CI.15.223; 7.CI.15.240; 7.CI.15.244; 7.CI.15.243; 7.CI.15.247; 7.CI.16.157; 7.CI.16.158; 7.CI.16.196; 7.CI.16.223; 7.CI.16.240; 7.CI.16.244; 7.CI.16.243; 7.CI.16.247; 7.CI.18.157; 7.CI.18.158; 7.CI.18.196; 7.CI.18.223; 7.CI.18.240; 7.CI.18.244; 7.CI.18.243; 7.CI.18.247; 7.CI.26.157; 7.CI.26.158; 7.CI.26.196; 7.CI.26.223; 7.CI.26.240; 7.CI.26.244; 7.CI.26.243; 7.CI.26.247; 7.CI.27.157; 7.CI.27.158; 7.CI.27.196; 7.CI.27.223; 7.CI.27.240; 7.CI.27.244; 7.CI.27.243; 7.CI.27.247; 7.CI.29.157; 7.CI.29.158; 7.CI.29.196; 7.CI.29.223; 7.CI.29.240; 7.CI.29.244; 7.CI.29.243; 7.CI.29.247; 7.CI.54.157; 7.CI.54.158; 7.CI.54.196; 7.CI.54.223; 7.CI.54.240; 7.CI.54.244; 7.CI.54.243; 7.CI.54.247; 7.CI.55.157; 7.CI.55.158; 7.CI.55.196; 7.CI.55.223; 7.CI.55.240; 7.CI.55.244; 7.CI.55.243; 7.CI.55.247; 7.CI.56.157; 7.CI.56.158; 7.CI.56.196; 7.CI.56.223; 7.CI.56.240; 7.CI.56.244; 7.CI.56.243; 7.CI.56.247; 7.CI.157.157; 7.CI.157.158; 7.CI.157.196; 7.CI.157.223; 7.CI.157.240; 7.CI.157.244; 7.CI.157.243; 7.CI.157.247; 7.CI.196.157; 7.CI.196.158; 7.CI.196.196; 7.CI.196.223; 7.CI.196.240; 7.CI.196.244; 7.CI.196.243; 7.CI.196.247; 7.CI.223.157; 7.CI.223.158; 7.CI.223.196; 7.CI.223.223; 7.CI.223.240; 7.CI.223.244; 7.CI.223.243; 7.CI.223.247; 7.CI.240.157; 7.CI.240.158; 7.CI.240.196; 7.CI.240.223; 7.CI.240.240; 7.CI.240.244; 7.CI.240.243; 7.CI.240.247; 7.CI.244.157; 7.CI.244.158; 7.CI.244.196; 7.CI.244.223; 7.CI.244.240; 7.CI.244.244; 7.CI.244.243; 7.CI.244.247; 7.CI.247.157; 7.CI.247.158; 7.CI.247.196; 7.CI.247.223; 7.CI.247.240; 7.CI.247.244; 7.CI.247.243; 7.CI.247.247;

Prodrugs of 7.CO

7.CO.4.157; 7.CO.4.158; 7.CO.4.196; 7.CO.4.223; 7.CO.4.240; 7.CO.4.244; 7.CO.4.243; 7.CO.4.247; 7.CO.5.157; 7.CO.5.158; 7.CO.5.196; 7.CO.5.223; 7.CO.5.240; 7.CO.5.244; 7.CO.5.243; 7.CO.5.247; 7.CO.7.157; 7.CO.7.158; 7.CO.7.196; 7.CO.7.223; 7.CO.7.240; 7.CO.7.244; 7.CO.7.243; 7.CO.7.247; 7.CO.15.157; 7.CO.15.158; 7.CO.15.196; 7.CO.15.223; 7.CO.15.240; 7.CO.15.244; 7.CO.15.243; 7.CO.15.247; 7.CO.16.157; 7.CO.16.158; 7.CO.16.196; 7.CO.16.223; 7.CO.16.240; 7.CO.16.244; 7.CO.16.243; 7.CO.16.247; 7.CO.18.157; 7.CO.18.158; 7.CO.18.196; 7.CO.18.223;

7.CO.18.240; 7.CO.18.244; 7.CO.18.243; 7.CO.18.247; 7.CO.26.157; 7.CO.26.158; 7.CO.26.196; 7.CO.26.223; 7.CO.26.240; 7.CO.26.244; 7.CO.26.243; 7.CO.26.247; 7.CO.27.157; 7.CO.27.158; 7.CO.27.196; 7.CO.27.223; 7.CO.27.240; 7.CO.27.244; 7.CO.27.243; 7.CO.27.247; 7.CO.29.157; 7.CO.29.158; 7.CO.29.196; 7.CO.29.223; 7.CO.29.240; 7.CO.29.244; 7.CO.29.243; 7.CO.29.247; 7.CO.54.157; 7.CO.54.158; 7.CO.54.196; 7.CO.54.223; 7.CO.54.240; 7.CO.54.244; 7.CO.54.243; 7.CO.54.247; 7.CO.55.157; 7.CO.55.158; 7.CO.55.196; 7.CO.55.223; 7.CO.55.240; 7.CO.55.244; 7.CO.55.243; 7.CO.55.247; 7.CO.56.157; 7.CO.56.158; 7.CO.56.196; 7.CO.56.223; 7.CO.56.240; 7.CO.56.244; 7.CO.56.243; 7.CO.56.247; 7.CO.157.157; 7.CO.157.158; 7.CO.157.196; 7.CO.157.223; 7.CO.157.240; 7.CO.157.244; 7.CO.157.243; 7.CO.157.247; 7.CO.196.157; 7.CO.196.158; 7.CO.196.196; 7.CO.196.223; 7.CO.196.240; 7.CO.196.244; 7.CO.196.243; 7.CO.196.247; 7.CO.223.157; 7.CO.223.158; 7.CO.223.196; 7.CO.223.223; 7.CO.223.240; 7.CO.223.244; 7.CO.223.243; 7.CO.223.247; 7.CO.240.157; 7.CO.240.158; 7.CO.240.196; 7.CO.240.223; 7.CO.240.240; 7.CO.240.244; 7.CO.240.243; 7.CO.240.247; 7.CO.244.157; 7.CO.244.158; 7.CO.244.196; 7.CO.244.223; 7.CO.244.240; 7.CO.244.244; 7.CO.244.243; 7.CO.244.247; 7.CO.4.157; 7.CO.4.158; 7.CO.4.196; 7.CO.4.223; 7.CO.4.240; 7.CO.4.244; 7.CO.4.243; 7.CO.4.247;

Prodrugs of 8.AH

8.AH.4.157; 8.AH.4.158; 8.AH.4.196; 8.AH.4.223; 8.AH.4.240; 8.AH.4.244; 8.AH.4.243; 8.AH.4.247; 8.AH.5.157; 8.AH.5.158; 8.AH.5.196; 8.AH.5.223; 8.AH.5.240; 8.AH.5.244; 8.AH.5.243; 8.AH.5.247; 8.AH.7.157; 8.AH.7.158; 8.AH.7.196; 8.AH.7.223; 8.AH.7.240; 8.AH.7.244; 8.AH.7.243; 8.AH.7.247; 8.AH.15.157; 8.AH.15.158; 8.AH.15.196; 8.AH.15.223; 8.AH.15.240; 8.AH.15.244; 8.AH.15.243; 8.AH.15.247; 8.AH.16.157; 8.AH.16.158; 8.AH.16.196; 8.AH.16.223; 8.AH.16.240; 8.AH.16.244; 8.AH.16.243; 8.AH.16.247; 8.AH.18.157; 8.AH.18.158; 8.AH.18.196; 8.AH.18.223; 8.AH.18.240; 8.AH.18.244; 8.AH.18.243; 8.AH.18.247; 8.AH.26.157; 8.AH.26.158; 8.AH.26.196; 8.AH.26.223; 8.AH.26.240; 8.AH.26.244;

8.AH.26.243; 8.AH.26.247; 8.AH.27.157; 8.AH.27.158; 8.AH.27.196; 8.AH.27.223; 8.AH.27.240; 8.AH.27.244; 8.AH.27.243; 8.AH.27.247; 8.AH.29.157; 8.AH.29.158; 8.AH.29.196; 8.AH.29.223; 8.AH.29.240; 8.AH.29.244; 8.AH.29.243; 8.AH.29.247; 8.AH.54.157; 8.AH.54.158; 8.AH.54.196; 8.AH.54.223; 8.AH.54.240; 8.AH.54.244; 8.AH.54.243; 8.AH.54.247; 8.AH.55.157; 8.AH.55.158; 8.AH.55.196; 8.AH.55.223; 8.AH.55.240; 8.AH.55.244; 8.AH.55.243; 8.AH.55.247; 8.AH.56.157; 8.AH.56.158; 8.AH.56.196; 8.AH.56.223; 8.AH.56.240; 8.AH.56.244; 8.AH.56.243; 8.AH.56.247; 8.AH.157.157; 8.AH.157.158; 8.AH.157.196; 8.AH.157.223; 8.AH.157.240; 8.AH.157.244; 8.AH.157.243; 8.AH.157.247; 8.AH.196.157; 8.AH.196.158; 8.AH.196.196; 8.AH.196.223; 8.AH.196.240; 8.AH.196.244; 8.AH.196.243; 8.AH.196.247; 8.AH.223.157; 8.AH.223.158; 8.AH.223.196; 8.AH.223.223; 8.AH.223.240; 8.AH.223.244; 8.AH.223.243; 8.AH.223.247; 8.AH.240.157; 8.AH.240.158; 8.AH.240.196; 8.AH.240.223; 8.AH.240.240; 8.AH.240.244; 8.AH.240.243; 8.AH.240.247; 8.AH.244.157; 8.AH.244.158; 8.AH.244.196; 8.AH.244.223; 8.AH.244.240; 8.AH.244.244; 8.AH.244.243; 8.AH.244.247; 8.AH.247.157; 8.AH.247.158; 8.AH.247.196; 8.AH.247.223; 8.AH.247.240; 8.AH.247.244; 8.AH.247.243; 8.AH.247.247;

Prodrugs of 8.AJ

8.AJ.4.157; 8.AJ.4.158; 8.AJ.4.196; 8.AJ.4.223; 8.AJ.4.240; 8.AJ.4.244; 8.AJ.4.243; 8.AJ.4.247; 8.AJ.5.157; 8.AJ.5.158; 8.AJ.5.196; 8.AJ.5.223; 8.AJ.5.240; 8.AJ.5.244; 8.AJ.5.243; 8.AJ.5.247; 8.AJ.7.157; 8.AJ.7.158; 8.AJ.7.196; 8.AJ.7.223; 8.AJ.7.240; 8.AJ.7.244; 8.AJ.7.243; 8.AJ.7.247; 8.AJ.15.157; 8.AJ.15.158; 8.AJ.15.196; 8.AJ.15.223; 8.AJ.15.240; 8.AJ.15.244; 8.AJ.15.243; 8.AJ.15.247; 8.AJ.16.157; 8.AJ.16.158; 8.AJ.16.196; 8.AJ.16.223; 8.AJ.16.240; 8.AJ.16.244; 8.AJ.16.243; 8.AJ.16.247; 8.AJ.18.157; 8.AJ.18.158; 8.AJ.18.196; 8.AJ.18.223; 8.AJ.18.240; 8.AJ.18.244; 8.AJ.18.243; 8.AJ.18.247; 8.AJ.26.157; 8.AJ.26.158; 8.AJ.26.196; 8.AJ.26.223; 8.AJ.26.240; 8.AJ.26.244; 8.AJ.26.243; 8.AJ.26.247; 8.AJ.27.157; 8.AJ.27.158; 8.AJ.27.196; 8.AJ.27.223; 8.AJ.27.240; 8.AJ.27.244; 8.AJ.27.243; 8.AJ.27.247; 8.AJ.29.157; 8.AJ.29.158; 8.AJ.29.196; 8.AJ.29.223; 8.AJ.29.240; 8.AJ.29.244; 8.AJ.29.243; 8.AJ.29.247;

8.AJ.54.157; 8.AJ.54.158; 8.AJ.54.196; 8.AJ.54.223; 8.AJ.54.240; 8.AJ.54.244; 8.AJ.54.243; 8.AJ.54.247; 8.AJ.55.157; 8.AJ.55.158; 8.AJ.55.196; 8.AJ.55.223; 8.AJ.55.240; 8.AJ.55.244; 8.AJ.55.243; 8.AJ.55.247; 8.AJ.56.157; 8.AJ.56.158; 8.AJ.56.196; 8.AJ.56.223; 8.AJ.56.240; 8.AJ.56.244; 8.AJ.56.243; 8.AJ.56.247; 8.AJ.157.157; 8.AJ.157.158; 8.AJ.157.196; 8.AJ.157.223; 8.AJ.157.240; 8.AJ.157.244; 8.AJ.157.243; 8.AJ.157.247; 8.AJ.196.157; 8.AJ.196.158; 8.AJ.196.196; 8.AJ.196.223; 8.AJ.196.240; 8.AJ.196.244; 8.AJ.196.243; 8.AJ.196.247; 8.AJ.223.157; 8.AJ.223.158; 8.AJ.223.196; 8.AJ.223.223; 8.AJ.223.240; 8.AJ.223.244; 8.AJ.223.243; 8.AJ.223.247; 8.AJ.240.157; 8.AJ.240.158; 8.AJ.240.196; 8.AJ.240.223; 8.AJ.240.240; 8.AJ.240.244; 8.AJ.240.243; 8.AJ.240.247; 8.AJ.244.157; 8.AJ.244.158; 8.AJ.244.196; 8.AJ.244.223; 8.AJ.244.240; 8.AJ.244.244; 8.AJ.244.243; 8.AJ.244.247; 8.AJ.247.157; 8.AJ.247.158; 8.AJ.247.196; 8.AJ.247.223; 8.AJ.247.240; 8.AJ.247.244; 8.AJ.247.243; 8.AJ.247.247;

Prodrugs of 8.AN

8.AN.4.157; 8.AN.4.158; 8.AN.4.196; 8.AN.4.223; 8.AN.4.240; 8.AN.4.244; 8.AN.4.243; 8.AN.4.247; 8.AN.5.157; 8.AN.5.158; 8.AN.5.196; 8.AN.5.223; 8.AN.5.240; 8.AN.5.244; 8.AN.5.243; 8.AN.5.247; 8.AN.7.157; 8.AN.7.158; 8.AN.7.196; 8.AN.7.223; 8.AN.7.240; 8.AN.7.244; 8.AN.7.243; 8.AN.7.247; 8.AN.15.157; 8.AN.15.158; 8.AN.15.196; 8.AN.15.223; 8.AN.15.240; 8.AN.15.244; 8.AN.15.243; 8.AN.15.247; 8.AN.16.157; 8.AN.16.158; 8.AN.16.196; 8.AN.16.223; 8.AN.16.240; 8.AN.16.244; 8.AN.16.243; 8.AN.16.247; 8.AN.18.157; 8.AN.18.158; 8.AN.18.196; 8.AN.18.223; 8.AN.18.240; 8.AN.18.244; 8.AN.18.243; 8.AN.18.247; 8.AN.26.157; 8.AN.26.158; 8.AN.26.196; 8.AN.26.223; 8.AN.26.240; 8.AN.26.244; 8.AN.26.243; 8.AN.26.247; 8.AN.27.157; 8.AN.27.158; 8.AN.27.196; 8.AN.27.223; 8.AN.27.240; 8.AN.27.244; 8.AN.27.243; 8.AN.27.247; 8.AN.29.157; 8.AN.29.158; 8.AN.29.196; 8.AN.29.223; 8.AN.29.240; 8.AN.29.244; 8.AN.29.243; 8.AN.29.247; 8.AN.54.157; 8.AN.54.158; 8.AN.54.196; 8.AN.54.223; 8.AN.54.240; 8.AN.54.244; 8.AN.54.243; 8.AN.54.247; 8.AN.55.157; 8.AN.55.158; 8.AN.55.196; 8.AN.55.223;

8.AN.55.240; 8.AN.55.244; 8.AN.55.243; 8.AN.55.247; 8.AN.56.157; 8.AN.56.158; 8.AN.56.196; 8.AN.56.223; 8.AN.56.240; 8.AN.56.244; 8.AN.56.243; 8.AN.56.247; 8.AN.157.157; 8.AN.157.158; 8.AN.157.196; 8.AN.157.223; 8.AN.157.240; 8.AN.157.244; 8.AN.157.243; 8.AN.157.247; 8.AN.196.157; 8.AN.196.158; 8.AN.196.196; 8.AN.196.223; 8.AN.196.240; 8.AN.196.244; 8.AN.196.243; 8.AN.196.247; 8.AN.223.157; 8.AN.223.158; 8.AN.223.196; 8.AN.223.223; 8.AN.223.240; 8.AN.223.244; 8.AN.223.243; 8.AN.223.247; 8.AN.240.157; 8.AN.240.158; 8.AN.240.196; 8.AN.240.223; 8.AN.240.240; 8.AN.240.244; 8.AN.240.243; 8.AN.240.247; 8.AN.244.157; 8.AN.244.158; 8.AN.244.196; 8.AN.244.223; 8.AN.244.240; 8.AN.244.244; 8.AN.244.243; 8.AN.244.247; 8.AN.247.157; 8.AN.247.158; 8.AN.247.196; 8.AN.247.223; 8.AN.247.240; 8.AN.247.244; 8.AN.247.243; 8.AN.247.247;

Prodrugs of 8.AP

8.AP.4.157; 8.AP.4.158; 8.AP.4.196; 8.AP.4.223; 8.AP.4.240; 8.AP.4.244; 8.AP.4.243; 8.AP.4.247; 8.AP.5.157; 8.AP.5.158; 8.AP.5.196; 8.AP.5.223; 8.AP.5.240; 8.AP.5.244; 8.AP.5.243; 8.AP.5.247; 8.AP.7.157; 8.AP.7.158; 8.AP.7.196; 8.AP.7.223; 8.AP.7.240; 8.AP.7.244; 8.AP.7.243; 8.AP.7.247; 8.AP.15.157; 8.AP.15.158; 8.AP.15.196; 8.AP.15.223; 8.AP.15.240; 8.AP.15.244; 8.AP.15.243; 8.AP.15.247; 8.AP.16.157; 8.AP.16.158; 8.AP.16.196; 8.AP.16.223; 8.AP.16.240; 8.AP.16.244; 8.AP.16.243; 8.AP.16.247; 8.AP.18.157; 8.AP.18.158; 8.AP.18.196; 8.AP.18.223; 8.AP.18.240; 8.AP.18.244; 8.AP.18.243; 8.AP.18.247; 8.AP.26.157; 8.AP.26.158; 8.AP.26.196; 8.AP.26.223; 8.AP.26.240; 8.AP.26.244; 8.AP.26.243; 8.AP.26.247; 8.AP.27.157; 8.AP.27.158; 8.AP.27.196; 8.AP.27.223; 8.AP.27.240; 8.AP.27.244; 8.AP.27.243; 8.AP.27.247; 8.AP.29.157; 8.AP.29.158; 8.AP.29.196; 8.AP.29.223; 8.AP.29.240; 8.AP.29.244; 8.AP.29.243; 8.AP.29.247; 8.AP.54.157; 8.AP.54.158; 8.AP.54.196; 8.AP.54.223; 8.AP.54.240; 8.AP.54.244; 8.AP.54.243; 8.AP.54.247; 8.AP.55.157; 8.AP.55.158; 8.AP.55.196; 8.AP.55.223; 8.AP.55.240; 8.AP.55.244; 8.AP.55.243; 8.AP.55.247; 8.AP.56.157; 8.AP.56.158; 8.AP.56.196; 8.AP.56.223; 8.AP.56.240; 8.AP.56.244;

8.AP.56.243; 8.AP.56.247; 8.AP.157.157; 8.AP.157.158; 8.AP.157.196; 8.AP.157.223; 8.AP.157.240; 8.AP.157.244; 8.AP.157.243; 8.AP.157.247; 8.AP.196.157; 8.AP.196.158; 8.AP.196.196; 8.AP.196.223; 8.AP.196.240; 8.AP.196.244; 8.AP.196.243; 8.AP.196.247; 8.AP.223.157; 8.AP.223.158; 8.AP.223.196; 8.AP.223.223; 8.AP.223.240; 8.AP.223.244; 8.AP.223.243; 8.AP.223.247; 8.AP.240.157; 8.AP.240.158; 8.AP.240.196; 8.AP.240.223; 8.AP.240.240; 8.AP.240.244; 8.AP.240.243; 8.AP.240.247; 8.AP.244.157; 8.AP.244.158; 8.AP.244.196; 8.AP.244.223; 8.AP.244.240; 8.AP.244.244; 8.AP.244.243; 8.AP.244.247; 8.AP.247.157; 8.AP.247.158; 8.AP.247.196; 8.AP.247.223; 8.AP.247.240; 8.AP.247.244; 8.AP.247.243; 8.AP.247.247;

Prodrugs of 8.AZ

8.AZ.4.157; 8.AZ.4.158; 8.AZ.4.196; 8.AZ.4.223; 8.AZ.4.240; 8.AZ.4.244; 8.AZ.4.243; 8.AZ.4.247; 8.AZ.5.157; 8.AZ.5.158; 8.AZ.5.196; 8.AZ.5.223; 8.AZ.5.240; 8.AZ.5.244; 8.AZ.5.243; 8.AZ.5.247; 8.AZ.7.157; 8.AZ.7.158; 8.AZ.7.196; 8.AZ.7.223; 8.AZ.7.240; 8.AZ.7.244; 8.AZ.7.243; 8.AZ.7.247; 8.AZ.15.157; 8.AZ.15.158; 8.AZ.15.196; 8.AZ.15.223; 8.AZ.15.240; 8.AZ.15.244; 8.AZ.15.243; 8.AZ.15.247; 8.AZ.16.157; 8.AZ.16.158; 8.AZ.16.196; 8.AZ.16.223; 8.AZ.16.240; 8.AZ.16.244; 8.AZ.16.243; 8.AZ.16.247; 8.AZ.18.157; 8.AZ.18.158; 8.AZ.18.196; 8.AZ.18.223; 8.AZ.18.240; 8.AZ.18.244; 8.AZ.18.243; 8.AZ.18.247; 8.AZ.26.157; 8.AZ.26.158; 8.AZ.26.196; 8.AZ.26.223; 8.AZ.26.240; 8.AZ.26.244; 8.AZ.26.243; 8.AZ.26.247; 8.AZ.27.157; 8.AZ.27.158; 8.AZ.27.196; 8.AZ.27.223; 8.AZ.27.240; 8.AZ.27.244; 8.AZ.27.243; 8.AZ.27.247; 8.AZ.29.157; 8.AZ.29.158; 8.AZ.29.196; 8.AZ.29.223; 8.AZ.29.240; 8.AZ.29.244; 8.AZ.29.243; 8.AZ.29.247; 8.AZ.54.157; 8.AZ.54.158; 8.AZ.54.196; 8.AZ.54.223; 8.AZ.54.240; 8.AZ.54.244; 8.AZ.54.243; 8.AZ.54.247; 8.AZ.55.157; 8.AZ.55.158; 8.AZ.55.196; 8.AZ.55.223; 8.AZ.55.240; 8.AZ.55.244; 8.AZ.55.243; 8.AZ.55.247; 8.AZ.56.157; 8.AZ.56.158; 8.AZ.56.196; 8.AZ.56.223; 8.AZ.56.240; 8.AZ.56.244; 8.AZ.56.243; 8.AZ.56.247; 8.AZ.157.157; 8.AZ.157.158; 8.AZ.157.196; 8.AZ.157.223; 8.AZ.157.240; 8.AZ.157.244; 8.AZ.157.243; 8.AZ.157.247;

8.AZ.196.157; 8.AZ.196.158; 8.AZ.196.196; 8.AZ.196.223; 8.AZ.196.240; 8.AZ.196.244; 8.AZ.196.243; 8.AZ.196.247; 8.AZ.223.157; 8.AZ.223.158; 8.AZ.223.196; 8.AZ.223.223; 8.AZ.223.240; 8.AZ.223.244; 8.AZ.223.243; 8.AZ.223.247; 8.AZ.240.157; 8.AZ.240.158; 8.AZ.240.196; 8.AZ.240.223; 8.AZ.240.240; 8.AZ.240.244; 8.AZ.240.243; 8.AZ.240.247; 8.AZ.244.157; 8.AZ.244.158; 8.AZ.244.196; 8.AZ.244.223; 8.AZ.244.240; 8.AZ.244.244; 8.AZ.244.243; 8.AZ.244.247; 8.AZ.247.157; 8.AZ.247.158; 8.AZ.247.196; 8.AZ.247.223; 8.AZ.247.240; 8.AZ.247.244; 8.AZ.247.243; 8.AZ.247.247;

Prodrugs of 8.BF

8.BF.4.157; 8.BF.4.158; 8.BF.4.196; 8.BF.4.223; 8.BF.4.240; 8.BF.4.244; 8.BF.4.243; 8.BF.4.247; 8.BF.5.157; 8.BF.5.158; 8.BF.5.196; 8.BF.5.223; 8.BF.5.240; 8.BF.5.244; 8.BF.5.243; 8.BF.5.247; 8.BF.7.157; 8.BF.7.158; 8.BF.7.196; 8.BF.7.223; 8.BF.7.240; 8.BF.7.244; 8.BF.7.243; 8.BF.7.247; 8.BF.15.157; 8.BF.15.158; 8.BF.15.196; 8.BF.15.223; 8.BF.15.240; 8.BF.15.244; 8.BF.15.243; 8.BF.15.247; 8.BF.16.157; 8.BF.16.158; 8.BF.16.196; 8.BF.16.223; 8.BF.16.240; 8.BF.16.244; 8.BF.16.243; 8.BF.16.247; 8.BF.18.157; 8.BF.18.158; 8.BF.18.196; 8.BF.18.223; 8.BF.18.240; 8.BF.18.244; 8.BF.18.243; 8.BF.18.247; 8.BF.26.157; 8.BF.26.158; 8.BF.26.196; 8.BF.26.223; 8.BF.26.240; 8.BF.26.244; 8.BF.26.243; 8.BF.26.247; 8.BF.27.157; 8.BF.27.158; 8.BF.27.196; 8.BF.27.223; 8.BF.27.240; 8.BF.27.244; 8.BF.27.243; 8.BF.27.247; 8.BF.29.157; 8.BF.29.158; 8.BF.29.196; 8.BF.29.223; 8.BF.29.240; 8.BF.29.244; 8.BF.29.243; 8.BF.29.247; 8.BF.54.157; 8.BF.54.158; 8.BF.54.196; 8.BF.54.223; 8.BF.54.240; 8.BF.54.244; 8.BF.54.243; 8.BF.54.247; 8.BF.55.157; 8.BF.55.158; 8.BF.55.196; 8.BF.55.223; 8.BF.55.240; 8.BF.55.244; 8.BF.55.243; 8.BF.55.247; 8.BF.56.157; 8.BF.56.158; 8.BF.56.196; 8.BF.56.223; 8.BF.56.240; 8.BF.56.244; 8.BF.56.243; 8.BF.56.247; 8.BF.157.157; 8.BF.157.158; 8.BF.157.196; 8.BF.157.223; 8.BF.157.240; 8.BF.157.244; 8.BF.157.243; 8.BF.157.247; 8.BF.196.157; 8.BF.196.158; 8.BF.196.196; 8.BF.196.223; 8.BF.196.240; 8.BF.196.244; 8.BF.196.243; 8.BF.196.247; 8.BF.223.157; 8.BF.223.158;

8.BF.223.196; 8.BF.223.223; 8.BF.223.240; 8.BF.223.244; 8.BF.223.243; 8.BF.223.247; 8.BF.240.157; 8.BF.240.158; 8.BF.240.196; 8.BF.240.223; 8.BF.240.240; 8.BF.240.244; 8.BF.240.243; 8.BF.240.247; 8.BF.244.157; 8.BF.244.158; 8.BF.244.196; 8.BF.244.223; 8.BF.244.240; 8.BF.244.244; 8.BF.244.243; 8.BF.244.247; 8.BF.247.157; 8.BF.247.158; 8.BF.247.196; 8.BF.247.223; 8.BF.247.240; 8.BF.247.244; 8.BF.247.243; 8.BF.247.247;

Prodrugs of 8.CI

8.CI.4.157; 8.CI.4.158; 8.CI.4.196; 8.CI.4.223; 8.CI.4.240; 8.CI.4.244; 8.CI.4.243; 8.CI.4.247; 8.CI.5.157; 8.CI.5.158; 8.CI.5.196; 8.CI.5.223; 8.CI.5.240; 8.CI.5.244; 8.CI.5.243; 8.CI.5.247; 8.CI.7.157; 8.CI.7.158; 8.CI.7.196; 8.CI.7.223; 8.CI.7.240; 8.CI.7.244; 8.CI.7.243; 8.CI.7.247; 8.CI.15.157; 8.CI.15.158; 8.CI.15.196; 8.CI.15.223; 8.CI.15.240; 8.CI.15.244; 8.CI.15.243; 8.CI.15.247; 8.CI.16.157; 8.CI.16.158; 8.CI.16.196; 8.CI.16.223; 8.CI.16.240; 8.CI.16.244; 8.CI.16.243; 8.CI.16.247; 8.CI.18.157; 8.CI.18.158; 8.CI.18.196; 8.CI.18.223; 8.CI.18.240; 8.CI.18.244; 8.CI.18.243; 8.CI.18.247; 8.CI.26.157; 8.CI.26.158; 8.CI.26.196; 8.CI.26.223; 8.CI.26.240; 8.CI.26.244; 8.CI.26.243; 8.CI.26.247; 8.CI.27.157; 8.CI.27.158; 8.CI.27.196; 8.CI.27.223; 8.CI.27.240; 8.CI.27.244; 8.CI.27.243; 8.CI.27.247; 8.CI.29.157; 8.CI.29.158; 8.CI.29.196; 8.CI.29.223; 8.CI.29.240; 8.CI.29.244; 8.CI.29.243; 8.CI.29.247; 8.CI.54.157; 8.CI.54.158; 8.CI.54.196; 8.CI.54.223; 8.CI.54.240; 8.CI.54.244; 8.CI.54.243; 8.CI.54.247; 8.CI.55.157; 8.CI.55.158; 8.CI.55.196; 8.CI.55.223; 8.CI.55.240; 8.CI.55.244; 8.CI.55.243; 8.CI.55.247; 8.CI.56.157; 8.CI.56.158; 8.CI.56.196; 8.CI.56.223; 8.CI.56.240; 8.CI.56.244; 8.CI.56.243; 8.CI.56.247; 8.CI.157.157; 8.CI.157.158; 8.CI.157.196; 8.CI.157.223; 8.CI.157.240; 8.CI.157.244; 8.CI.157.243; 8.CI.157.247; 8.CI.196.157; 8.CI.196.158; 8.CI.196.196; 8.CI.196.223; 8.CI.196.240; 8.CI.196.244; 8.CI.196.243; 8.CI.196.247; 8.CI.223.157; 8.CI.223.158; 8.CI.223.196; 8.CI.223.223; 8.CI.223.240; 8.CI.223.244; 8.CI.223.243; 8.CI.223.247; 8.CI.240.157; 8.CI.240.158; 8.CI.240.196; 8.CI.240.223; 8.CI.240.240; 8.CI.240.244; 8.CI.240.243; 8.CI.240.247; 8.CI.244.157; 8.CI.244.158; 8.CI.244.196; 8.CI.244.223; 8.CI.244.240; 8.CI.244.244; 8.CI.244.243; 8.CI.244.247;

8.CI.247.157; 8.CI.247.158; 8.CI.247.196; 8.CI.247.223; 8.CI.247.240; 8.CI.247.244; 8.CI.247.243; 8.CI.247.247;

Prodrugs of 8.CO

8.CO.4.157; 8.CO.4.158; 8.CO.4.196; 8.CO.4.223; 8.CO.4.240; 8.CO.4.244; 8.CO.4.243; 8.CO.4.247; 8.CO.5.157; 8.CO.5.158; 8.CO.5.196; 8.CO.5.223; 8.CO.5.240; 8.CO.5.244; 8.CO.5.243; 8.CO.5.247; 8.CO.7.157; 8.CO.7.158; 8.CO.7.196; 8.CO.7.223; 8.CO.7.240; 8.CO.7.244; 8.CO.7.243; 8.CO.7.247; 8.CO.15.157; 8.CO.15.158; 8.CO.15.196; 8.CO.15.223; 8.CO.15.240; 8.CO.15.244; 8.CO.15.243; 8.CO.15.247; 8.CO.16.157; 8.CO.16.158; 8.CO.16.196; 8.CO.16.223; 8.CO.16.240; 8.CO.16.244; 8.CO.16.243; 8.CO.16.247; 8.CO.18.157; 8.CO.18.158; 8.CO.18.196; 8.CO.18.223; 8.CO.18.240; 8.CO.18.244; 8.CO.18.243; 8.CO.18.247; 8.CO.26.157; 8.CO.26.158; 8.CO.26.196; 8.CO.26.223; 8.CO.26.240; 8.CO.26.244; 8.CO.26.243; 8.CO.26.247; 8.CO.27.157; 8.CO.27.158; 8.CO.27.196; 8.CO.27.223; 8.CO.27.240; 8.CO.27.244; 8.CO.27.243; 8.CO.27.247; 8.CO.29.157; 8.CO.29.158; 8.CO.29.196; 8.CO.29.223; 8.CO.29.240; 8.CO.29.244; 8.CO.29.243; 8.CO.29.247; 8.CO.54.157; 8.CO.54.158; 8.CO.54.196; 8.CO.54.223; 8.CO.54.240; 8.CO.54.244; 8.CO.54.243; 8.CO.54.247; 8.CO.55.157; 8.CO.55.158; 8.CO.55.196; 8.CO.55.223; 8.CO.55.240; 8.CO.55.244; 8.CO.55.243; 8.CO.55.247; 8.CO.56.157; 8.CO.56.158; 8.CO.56.196; 8.CO.56.223; 8.CO.56.240; 8.CO.56.244; 8.CO.56.243; 8.CO.56.247; 8.CO.157.157; 8.CO.157.158; 8.CO.157.196; 8.CO.157.223; 8.CO.157.240; 8.CO.157.244; 8.CO.157.243; 8.CO.157.247; 8.CO.196.157; 8.CO.196.158; 8.CO.196.196; 8.CO.196.223; 8.CO.196.240; 8.CO.196.244; 8.CO.196.243; 8.CO.196.247; 8.CO.223.157; 8.CO.223.158; 8.CO.223.196; 8.CO.223.223; 8.CO.223.240; 8.CO.223.244; 8.CO.223.243; 8.CO.223.247; 8.CO.240.157; 8.CO.240.158; 8.CO.240.196; 8.CO.240.223; 8.CO.240.240; 8.CO.240.244; 8.CO.240.243; 8.CO.240.247; 8.CO.244.157; 8.CO.244.158; 8.CO.244.196; 8.CO.244.223; 8.CO.244.240; 8.CO.244.244; 8.CO.244.243; 8.CO.244.247; 8.CO.247.157; 8.CO.247.158; 8.CO.247.196; 8.CO.247.223; 8.CO.247.240; 8.CO.247.244; 8.CO.247.243; 8.CO.247.247;

Prodrugs of 9.AH

9.AH.4.157; 9.AH.4.158; 9.AH.4.196; 9.AH.4.223; 9.AH.4.240; 9.AH.4.244; 9.AH.4.243; 9.AH.4.247; 9.AH.5.157; 9.AH.5.158; 9.AH.5.196; 9.AH.5.223; 9.AH.5.240; 9.AH.5.244; 9.AH.5.243; 9.AH.5.247; 9.AH.7.157; 9.AH.7.158; 9.AH.7.196; 9.AH.7.223; 9.AH.7.240; 9.AH.7.244; 9.AH.7.243; 9.AH.7.247; 9.AH.15.157; 9.AH.15.158; 9.AH.15.196; 9.AH.15.223; 9.AH.15.240; 9.AH.15.244; 9.AH.15.243; 9.AH.15.247; 9.AH.16.157; 9.AH.16.158; 9.AH.16.196; 9.AH.16.223; 9.AH.16.240; 9.AH.16.244; 9.AH.16.243; 9.AH.16.247; 9.AH.18.157; 9.AH.18.158; 9.AH.18.196; 9.AH.18.223; 9.AH.18.240; 9.AH.18.244; 9.AH.18.243; 9.AH.18.247; 9.AH.26.157; 9.AH.26.158; 9.AH.26.196; 9.AH.26.223; 9.AH.26.240; 9.AH.26.244; 9.AH.26.243; 9.AH.26.247; 9.AH.27.157; 9.AH.27.158; 9.AH.27.196; 9.AH.27.223; 9.AH.27.240; 9.AH.27.244; 9.AH.27.243; 9.AH.27.247; 9.AH.29.157; 9.AH.29.158; 9.AH.29.196; 9.AH.29.223; 9.AH.29.240; 9.AH.29.244; 9.AH.29.243; 9.AH.29.247; 9.AH.54.157; 9.AH.54.158; 9.AH.54.196; 9.AH.54.223; 9.AH.54.240; 9.AH.54.244; 9.AH.54.243; 9.AH.54.247; 9.AH.55.157; 9.AH.55.158; 9.AH.55.196; 9.AH.55.223; 9.AH.55.240; 9.AH.55.244; 9.AH.55.243; 9.AH.55.247; 9.AH.56.157; 9.AH.56.158; 9.AH.56.196; 9.AH.56.223; 9.AH.56.240; 9.AH.56.244; 9.AH.56.243; 9.AH.56.247; 9.AH.157.157; 9.AH.157.158; 9.AH.157.196; 9.AH.157.223; 9.AH.157.240; 9.AH.157.244; 9.AH.157.243; 9.AH.157.247; 9.AH.196.157; 9.AH.196.158; 9.AH.196.196; 9.AH.196.223; 9.AH.196.240; 9.AH.196.244; 9.AH.196.243; 9.AH.196.247; 9.AH.223.157; 9.AH.223.158; 9.AH.223.196; 9.AH.223.223; 9.AH.223.240; 9.AH.223.244; 9.AH.223.243; 9.AH.223.247; 9.AH.240.157; 9.AH.240.158; 9.AH.240.196; 9.AH.240.223; 9.AH.240.240; 9.AH.240.244; 9.AH.240.243; 9.AH.240.247; 9.AH.244.157; 9.AH.244.158; 9.AH.244.196; 9.AH.244.223; 9.AH.244.240; 9.AH.244.244; 9.AH.244.243; 9.AH.244.247; 9.AH.247.157; 9.AH.247.158; 9.AH.247.196; 9.AH.247.223; 9.AH.247.240; 9.AH.247.244; 9.AH.247.243; 9.AH.247.247;

Prodrugs of 9.AJ

9.AJ.4.157; 9.AJ.4.158; 9.AJ.4.196; 9.AJ.4.223; 9.AJ.4.240; 9.AJ.4.244; 9.AJ.4.243; 9.AJ.4.247; 9.AJ.5.157; 9.AJ.5.158; 9.AJ.5.196; 9.AJ.5.223; 9.AJ.5.240; 9.AJ.5.244; 9.AJ.5.243; 9.AJ.5.247; 9.AJ.7.157; 9.AJ.7.158; 9.AJ.7.196; 9.AJ.7.223; 9.AJ.7.240; 9.AJ.7.244; 9.AJ.7.243; 9.AJ.7.247; 9.AJ.15.157; 9.AJ.15.158; 9.AJ.15.196; 9.AJ.15.223; 9.AJ.15.240; 9.AJ.15.244; 9.AJ.15.243; 9.AJ.15.247; 9.AJ.16.157; 9.AJ.16.158; 9.AJ.16.196; 9.AJ.16.223; 9.AJ.16.240; 9.AJ.16.244; 9.AJ.16.243; 9.AJ.16.247; 9.AJ.18.157; 9.AJ.18.158; 9.AJ.18.196; 9.AJ.18.223; 9.AJ.18.240; 9.AJ.18.244; 9.AJ.18.243; 9.AJ.18.247; 9.AJ.26.157; 9.AJ.26.158; 9.AJ.26.196; 9.AJ.26.223; 9.AJ.26.240; 9.AJ.26.244; 9.AJ.26.243; 9.AJ.26.247; 9.AJ.27.157; 9.AJ.27.158; 9.AJ.27.196; 9.AJ.27.223; 9.AJ.27.240; 9.AJ.27.244; 9.AJ.27.243; 9.AJ.27.247; 9.AJ.29.157; 9.AJ.29.158; 9.AJ.29.196; 9.AJ.29.223; 9.AJ.29.240; 9.AJ.29.244; 9.AJ.29.243; 9.AJ.29.247; 9.AJ.54.157; 9.AJ.54.158; 9.AJ.54.196; 9.AJ.54.223; 9.AJ.54.240; 9.AJ.54.244; 9.AJ.54.243; 9.AJ.54.247; 9.AJ.55.157; 9.AJ.55.158; 9.AJ.55.196; 9.AJ.55.223; 9.AJ.55.240; 9.AJ.55.244; 9.AJ.55.243; 9.AJ.55.247; 9.AJ.56.157; 9.AJ.56.158; 9.AJ.56.196; 9.AJ.56.223; 9.AJ.56.240; 9.AJ.56.244; 9.AJ.56.243; 9.AJ.56.247; 9.AJ.157.157; 9.AJ.157.158; 9.AJ.157.196; 9.AJ.157.223; 9.AJ.157.240; 9.AJ.157.244; 9.AJ.157.243; 9.AJ.157.247; 9.AJ.196.157; 9.AJ.196.158; 9.AJ.196.196; 9.AJ.196.223; 9.AJ.196.240; 9.AJ.196.244; 9.AJ.196.243; 9.AJ.196.247; 9.AJ.223.157; 9.AJ.223.158; 9.AJ.223.196; 9.AJ.223.223; 9.AJ.223.240; 9.AJ.223.244; 9.AJ.223.243; 9.AJ.223.247; 9.AJ.240.157; 9.AJ.240.158; 9.AJ.240.196; 9.AJ.240.223; 9.AJ.240.240; 9.AJ.240.244; 9.AJ.240.243; 9.AJ.240.247; 9.AJ.244.157; 9.AJ.244.158; 9.AJ.244.196; 9.AJ.244.223; 9.AJ.244.240; 9.AJ.244.244; 9.AJ.244.243; 9.AJ.244.247; 9.AJ.247.157; 9.AJ.247.158; 9.AJ.247.196; 9.AJ.247.223; 9.AJ.247.240; 9.AJ.247.244; 9.AJ.247.243; 9.AJ.247.247;

Prodrugs of 9.AN

9.AN.4.157; 9.AN.4.158; 9.AN.4.196; 9.AN.4.223; 9.AN.4.240; 9.AN.4.244; 9.AN.4.243; 9.AN.4.247; 9.AN.5.157; 9.AN.5.158; 9.AN.5.196; 9.AN.5.223; 9.AN.5.240; 9.AN.5.244; 9.AN.5.243; 9.AN.5.247; 9.AN.7.157; 9.AN.7.158; 9.AN.7.196; 9.AN.7.223; 9.AN.7.240; 9.AN.7.244; 9.AN.7.243; 9.AN.7.247;

9.AN.15.157; 9.AN.15.158; 9.AN.15.196; 9.AN.15.223; 9.AN.15.240; 9.AN.15.244; 9.AN.15.243; 9.AN.15.247; 9.AN.16.157; 9.AN.16.158; 9.AN.16.196; 9.AN.16.223; 9.AN.16.240; 9.AN.16.244; 9.AN.16.243; 9.AN.16.247; 9.AN.18.157; 9.AN.18.158; 9.AN.18.196; 9.AN.18.223; 9.AN.18.240; 9.AN.18.244; 9.AN.18.243; 9.AN.18.247; 9.AN.26.157; 9.AN.26.158; 9.AN.26.196; 9.AN.26.223; 9.AN.26.240; 9.AN.26.244; 9.AN.26.243; 9.AN.26.247; 9.AN.27.157; 9.AN.27.158; 9.AN.27.196; 9.AN.27.223; 9.AN.27.240; 9.AN.27.244; 9.AN.27.243; 9.AN.27.247; 9.AN.29.157; 9.AN.29.158; 9.AN.29.196; 9.AN.29.223; 9.AN.29.240; 9.AN.29.244; 9.AN.29.243; 9.AN.29.247; 9.AN.54.157; 9.AN.54.158; 9.AN.54.196; 9.AN.54.223; 9.AN.54.240; 9.AN.54.244; 9.AN.54.243; 9.AN.54.247; 9.AN.55.157; 9.AN.55.158; 9.AN.55.196; 9.AN.55.223; 9.AN.55.240; 9.AN.55.244; 9.AN.55.243; 9.AN.55.247; 9.AN.56.157; 9.AN.56.158; 9.AN.56.196; 9.AN.56.223; 9.AN.56.240; 9.AN.56.244; 9.AN.56.243; 9.AN.56.247; 9.AN.157.157; 9.AN.157.158; 9.AN.157.196; 9.AN.157.223; 9.AN.157.240; 9.AN.157.244; 9.AN.157.243; 9.AN.157.247; 9.AN.196.157; 9.AN.196.158; 9.AN.196.196; 9.AN.196.223; 9.AN.196.240; 9.AN.196.244; 9.AN.196.243; 9.AN.196.247; 9.AN.223.157; 9.AN.223.158; 9.AN.223.196; 9.AN.223.223; 9.AN.223.240; 9.AN.223.244; 9.AN.223.243; 9.AN.223.247; 9.AN.240.157; 9.AN.240.158; 9.AN.240.196; 9.AN.240.223; 9.AN.240.240; 9.AN.240.244; 9.AN.240.243; 9.AN.240.247; 9.AN.244.157; 9.AN.244.158; 9.AN.244.196; 9.AN.244.223; 9.AN.244.240; 9.AN.244.244; 9.AN.244.243; 9.AN.244.247; 9.AN.247.157; 9.AN.247.158; 9.AN.247.196; 9.AN.247.223; 9.AN.247.240; 9.AN.247.244; 9.AN.247.243; 9.AN.247.247;

Prodrugs of 9.AP

9.AP.4.157; 9.AP.4.158; 9.AP.4.196; 9.AP.4.223; 9.AP.4.240; 9.AP.4.244; 9.AP.4.243; 9.AP.4.247; 9.AP.5.157; 9.AP.5.158; 9.AP.5.196; 9.AP.5.223; 9.AP.5.240; 9.AP.5.244; 9.AP.5.243; 9.AP.5.247; 9.AP.7.157; 9.AP.7.158; 9.AP.7.196; 9.AP.7.223; 9.AP.7.240; 9.AP.7.244; 9.AP.7.243; 9.AP.7.247; 9.AP.15.157; 9.AP.15.158; 9.AP.15.196; 9.AP.15.223; 9.AP.15.240; 9.AP.15.244; 9.AP.15.243; 9.AP.15.247; 9.AP.16.157; 9.AP.16.158;

9.AP.16.196; 9.AP.16.223; 9.AP.16.240; 9.AP.16.244; 9.AP.16.243; 9.AP.16.247; 9.AP.18.157; 9.AP.18.158; 9.AP.18.196; 9.AP.18.223; 9.AP.18.240; 9.AP.18.244; 9.AP.18.243; 9.AP.18.247; 9.AP.26.157; 9.AP.26.158; 9.AP.26.196; 9.AP.26.223; 9.AP.26.240; 9.AP.26.244; 9.AP.26.243; 9.AP.26.247; 9.AP.27.157; 9.AP.27.158; 9.AP.27.196; 9.AP.27.223; 9.AP.27.240; 9.AP.27.244; 9.AP.27.243; 9.AP.27.247; 9.AP.29.157; 9.AP.29.158; 9.AP.29.196; 9.AP.29.223; 9.AP.29.240; 9.AP.29.244; 9.AP.29.243; 9.AP.29.247; 9.AP.54.157; 9.AP.54.158; 9.AP.54.196; 9.AP.54.223; 9.AP.54.240; 9.AP.54.244; 9.AP.54.243; 9.AP.54.247; 9.AP.55.157; 9.AP.55.158; 9.AP.55.196; 9.AP.55.223; 9.AP.55.240; 9.AP.55.244; 9.AP.55.243; 9.AP.55.247; 9.AP.56.157; 9.AP.56.158; 9.AP.56.196; 9.AP.56.223; 9.AP.56.240; 9.AP.56.244; 9.AP.56.243; 9.AP.56.247; 9.AP.157.157; 9.AP.157.158; 9.AP.157.196; 9.AP.157.223; 9.AP.157.240; 9.AP.157.244; 9.AP.157.243; 9.AP.157.247; 9.AP.196.157; 9.AP.196.158; 9.AP.196.196; 9.AP.196.223; 9.AP.196.240; 9.AP.196.244; 9.AP.196.243; 9.AP.196.247; 9.AP.223.157; 9.AP.223.158; 9.AP.223.196; 9.AP.223.223; 9.AP.223.240; 9.AP.223.244; 9.AP.223.243; 9.AP.223.247; 9.AP.240.157; 9.AP.240.158; 9.AP.240.196; 9.AP.240.223; 9.AP.240.240; 9.AP.240.244; 9.AP.240.243; 9.AP.240.247; 9.AP.244.157; 9.AP.244.158; 9.AP.244.196; 9.AP.244.223; 9.AP.244.240; 9.AP.244.244; 9.AP.244.243; 9.AP.244.247; 9.AP.247.157; 9.AP.247.158; 9.AP.247.196; 9.AP.247.223; 9.AP.247.240; 9.AP.247.244; 9.AP.247.243; 9.AP.247.247;

Prodrugs of 9.AZ

9.AZ.4.157; 9.AZ.4.158; 9.AZ.4.196; 9.AZ.4.223; 9.AZ.4.240; 9.AZ.4.244; 9.AZ.4.243; 9.AZ.4.247; 9.AZ.5.157; 9.AZ.5.158; 9.AZ.5.196; 9.AZ.5.223; 9.AZ.5.240; 9.AZ.5.244; 9.AZ.5.243; 9.AZ.5.247; 9.AZ.7.157; 9.AZ.7.158; 9.AZ.7.196; 9.AZ.7.223; 9.AZ.7.240; 9.AZ.7.244; 9.AZ.7.243; 9.AZ.7.247; 9.AZ.15.157; 9.AZ.15.158; 9.AZ.15.196; 9.AZ.15.223; 9.AZ.15.240; 9.AZ.15.244; 9.AZ.15.243; 9.AZ.15.247; 9.AZ.16.157; 9.AZ.16.158; 9.AZ.16.196; 9.AZ.16.223; 9.AZ.16.240; 9.AZ.16.244; 9.AZ.16.243; 9.AZ.16.247; 9.AZ.18.157; 9.AZ.18.158; 9.AZ.18.196; 9.AZ.18.223;

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Prodrugs of 9.BF

9.BF.4.157; 9.BF.4.158; 9.BF.4.196; 9.BF.4.223; 9.BF.4.240; 9.BF.4.244; 9.BF.4.243; 9.BF.4.247; 9.BF.5.157; 9.BF.5.158; 9.BF.5.196; 9.BF.5.223; 9.BF.5.240; 9.BF.5.244; 9.BF.5.243; 9.BF.5.247; 9.BF.7.157; 9.BF.7.158; 9.BF.7.196; 9.BF.7.223; 9.BF.7.240; 9.BF.7.244; 9.BF.7.243; 9.BF.7.247; 9.BF.15.157; 9.BF.15.158; 9.BF.15.196; 9.BF.15.223; 9.BF.15.240; 9.BF.15.244; 9.BF.15.243; 9.BF.15.247; 9.BF.16.157; 9.BF.16.158; 9.BF.16.196; 9.BF.16.223; 9.BF.16.240; 9.BF.16.244; 9.BF.16.243; 9.BF.16.247; 9.BF.18.157; 9.BF.18.158; 9.BF.18.196; 9.BF.18.223; 9.BF.18.240; 9.BF.18.244; 9.BF.18.243; 9.BF.18.247; 9.BF.26.157; 9.BF.26.158; 9.BF.26.196; 9.BF.26.223; 9.BF.26.240; 9.BF.26.244;

9.BF.26.243; 9.BF.26.247; 9.BF.27.157; 9.BF.27.158; 9.BF.27.196; 9.BF.27.223; 9.BF.27.240; 9.BF.27.244; 9.BF.27.243; 9.BF.27.247; 9.BF.29.157; 9.BF.29.158; 9.BF.29.196; 9.BF.29.223; 9.BF.29.240; 9.BF.29.244; 9.BF.29.243; 9.BF.29.247; 9.BF.54.157; 9.BF.54.158; 9.BF.54.196; 9.BF.54.223; 9.BF.54.240; 9.BF.54.244; 9.BF.54.243; 9.BF.54.247; 9.BF.55.157; 9.BF.55.158; 9.BF.55.196; 9.BF.55.223; 9.BF.55.240; 9.BF.55.244; 9.BF.55.243; 9.BF.55.247; 9.BF.56.157; 9.BF.56.158; 9.BF.56.196; 9.BF.56.223; 9.BF.56.240; 9.BF.56.244; 9.BF.56.243; 9.BF.56.247; 9.BF.157.157; 9.BF.157.158; 9.BF.157.196; 9.BF.157.223; 9.BF.157.240; 9.BF.157.244; 9.BF.157.243; 9.BF.157.247; 9.BF.196.157; 9.BF.196.158; 9.BF.196.196; 9.BF.196.223; 9.BF.196.240; 9.BF.196.244; 9.BF.196.243; 9.BF.196.247; 9.BF.223.157; 9.BF.223.158; 9.BF.223.196; 9.BF.223.223; 9.BF.223.240; 9.BF.223.244; 9.BF.223.243; 9.BF.223.247; 9.BF.240.157; 9.BF.240.158; 9.BF.240.196; 9.BF.240.223; 9.BF.240.240; 9.BF.240.244; 9.BF.240.243; 9.BF.240.247; 9.BF.244.157; 9.BF.244.158; 9.BF.244.196; 9.BF.244.223; 9.BF.244.240; 9.BF.244.244; 9.BF.244.243; 9.BF.244.247; 9.BF.247.157; 9.BF.247.158; 9.BF.247.196; 9.BF.247.223; 9.BF.247.240; 9.BF.247.244; 9.BF.247.243; 9.BF.247.247;

Prodrugs of 9.CI

9.CI.4.157; 9.CI.4.158; 9.CI.4.196; 9.CI.4.223; 9.CI.4.240; 9.CI.4.244; 9.CI.4.243; 9.CI.4.247; 9.CI.5.157; 9.CI.5.158; 9.CI.5.196; 9.CI.5.223; 9.CI.5.240; 9.CI.5.244; 9.CI.5.243; 9.CI.5.247; 9.CI.7.157; 9.CI.7.158; 9.CI.7.196; 9.CI.7.223; 9.CI.7.240; 9.CI.7.244; 9.CI.7.243; 9.CI.7.247; 9.CI.15.157; 9.CI.15.158; 9.CI.15.196; 9.CI.15.223; 9.CI.15.240; 9.CI.15.244; 9.CI.15.243; 9.CI.15.247; 9.CI.16.157; 9.CI.16.158; 9.CI.16.196; 9.CI.16.223; 9.CI.16.240; 9.CI.16.244; 9.CI.16.243; 9.CI.16.247; 9.CI.18.157; 9.CI.18.158; 9.CI.18.196; 9.CI.18.223; 9.CI.18.240; 9.CI.18.244; 9.CI.18.243; 9.CI.18.247; 9.CI.26.157; 9.CI.26.158; 9.CI.26.196; 9.CI.26.223; 9.CI.26.240; 9.CI.26.244; 9.CI.26.243; 9.CI.26.247; 9.CI.27.157; 9.CI.27.158; 9.CI.27.196; 9.CI.27.223; 9.CI.27.240; 9.CI.27.244; 9.CI.27.243; 9.CI.27.247; 9.CI.29.157; 9.CI.29.158; 9.CI.29.196; 9.CI.29.223; 9.CI.29.240; 9.CI.29.244; 9.CI.29.243; 9.CI.29.247;

9.CI.54.157; 9.CI.54.158; 9.CI.54.196; 9.CI.54.223; 9.CI.54.240; 9.CI.54.244; 9.CI.54.243; 9.CI.54.247; 9.CI.55.157; 9.CI.55.158; 9.CI.55.196; 9.CI.55.223; 9.CI.55.240; 9.CI.55.244; 9.CI.55.243; 9.CI.55.247; 9.CI.56.157; 9.CI.56.158; 9.CI.56.196; 9.CI.56.223; 9.CI.56.240; 9.CI.56.244; 9.CI.56.243; 9.CI.56.247; 9.CI.157.157; 9.CI.157.158; 9.CI.157.196; 9.CI.157.223; 9.CI.157.240; 9.CI.157.244; 9.CI.157.243; 9.CI.157.247; 9.CI.196.157; 9.CI.196.158; 9.CI.196.196; 9.CI.196.223; 9.CI.196.240; 9.CI.196.244; 9.CI.196.243; 9.CI.196.247; 9.CI.223.157; 9.CI.223.158; 9.CI.223.196; 9.CI.223.223; 9.CI.223.240; 9.CI.223.244; 9.CI.223.243; 9.CI.223.247; 9.CI.240.157; 9.CI.240.158; 9.CI.240.196; 9.CI.240.223; 9.CI.240.240; 9.CI.240.244; 9.CI.240.243; 9.CI.240.247; 9.CI.244.157; 9.CI.244.158; 9.CI.244.196; 9.CI.244.223; 9.CI.244.240; 9.CI.244.244; 9.CI.244.243; 9.CI.244.247; 9.CI.247.157; 9.CI.247.158; 9.CI.247.196; 9.CI.247.223; 9.CI.247.240; 9.CI.247.244; 9.CI.247.243; 9.CI.247.247;

Prodrugs of 9.CO

9.CO.4.157; 9.CO.4.158; 9.CO.4.196; 9.CO.4.223; 9.CO.4.240; 9.CO.4.244; 9.CO.4.243; 9.CO.4.247; 9.CO.5.157; 9.CO.5.158; 9.CO.5.196; 9.CO.5.223; 9.CO.5.240; 9.CO.5.244; 9.CO.5.243; 9.CO.5.247; 9.CO.7.157; 9.CO.7.158; 9.CO.7.196; 9.CO.7.223; 9.CO.7.240; 9.CO.7.244; 9.CO.7.243; 9.CO.7.247; 9.CO.15.157; 9.CO.15.158; 9.CO.15.196; 9.CO.15.223; 9.CO.15.240; 9.CO.15.244; 9.CO.15.243; 9.CO.15.247; 9.CO.16.157; 9.CO.16.158; 9.CO.16.196; 9.CO.16.223; 9.CO.16.240; 9.CO.16.244; 9.CO.16.243; 9.CO.16.247; 9.CO.18.157; 9.CO.18.158; 9.CO.18.196; 9.CO.18.223; 9.CO.18.240; 9.CO.18.244; 9.CO.18.243; 9.CO.18.247; 9.CO.26.157; 9.CO.26.158; 9.CO.26.196; 9.CO.26.223; 9.CO.26.240; 9.CO.26.244; 9.CO.26.243; 9.CO.26.247; 9.CO.27.157; 9.CO.27.158; 9.CO.27.196; 9.CO.27.223; 9.CO.27.240; 9.CO.27.244; 9.CO.27.243; 9.CO.27.247; 9.CO.29.157; 9.CO.29.158; 9.CO.29.196; 9.CO.29.223; 9.CO.29.240; 9.CO.29.244; 9.CO.29.243; 9.CO.29.247; 9.CO.54.157; 9.CO.54.158; 9.CO.54.196; 9.CO.54.223; 9.CO.54.240; 9.CO.54.244; 9.CO.54.243; 9.CO.54.247; 9.CO.55.157; 9.CO.55.158; 9.CO.55.196; 9.CO.55.223;

9.CO.55.240; 9.CO.55.244; 9.CO.55.243; 9.CO.55.247; 9.CO.56.157; 9.CO.56.158; 9.CO.56.196; 9.CO.56.223; 9.CO.56.240; 9.CO.56.244; 9.CO.56.243; 9.CO.56.247; 9.CO.157.157; 9.CO.157.158; 9.CO.157.196; 9.CO.157.223; 9.CO.157.240; 9.CO.157.244; 9.CO.157.243; 9.CO.157.247; 9.CO.196.157; 9.CO.196.158; 9.CO.196.196; 9.CO.196.223; 9.CO.196.240; 9.CO.196.244; 9.CO.196.243; 9.CO.196.247; 9.CO.223.157; 9.CO.223.158; 9.CO.223.196; 9.CO.223.223; 9.CO.223.240; 9.CO.223.244; 9.CO.223.243; 9.CO.223.247; 9.CO.240.157; 9.CO.240.158; 9.CO.240.196; 9.CO.240.223; 9.CO.240.240; 9.CO.240.244; 9.CO.240.243; 9.CO.240.247; 9.CO.244.157; 9.CO.244.158; 9.CO.244.196; 9.CO.244.223; 9.CO.244.240; 9.CO.244.244; 9.CO.244.243; 9.CO.244.247; 9.CO.247.157; 9.CO.247.158; 9.CO.247.196; 9.CO.247.223; 9.CO.247.240; 9.CO.247.244; 9.CO.247.243; 9.CO.247.247;

Prodrugs of 10.AH

10.AH.4.157; 10.AH.4.158; 10.AH.4.196; 10.AH.4.223; 10.AH.4.240; 10.AH.4.244; 10.AH.4.243; 10.AH.4.247; 10.AH.5.157; 10.AH.5.158; 10.AH.5.196; 10.AH.5.223; 10.AH.5.240; 10.AH.5.244; 10.AH.5.243; 10.AH.5.247; 10.AH.7.157; 10.AH.7.158; 10.AH.7.196; 10.AH.7.223; 10.AH.7.240; 10.AH.7.244; 10.AH.7.243; 10.AH.7.247; 10.AH.15.157; 10.AH.15.158; 10.AH.15.196; 10.AH.15.223; 10.AH.15.240; 10.AH.15.244; 10.AH.15.243; 10.AH.15.247; 10.AH.16.157; 10.AH.16.158; 10.AH.16.196; 10.AH.16.223; 10.AH.16.240; 10.AH.16.244; 10.AH.16.243; 10.AH.16.247; 10.AH.18.157; 10.AH.18.158; 10.AH.18.196; 10.AH.18.223; 10.AH.18.240; 10.AH.18.244; 10.AH.18.243; 10.AH.18.247; 10.AH.26.157; 10.AH.26.158; 10.AH.26.196; 10.AH.26.223; 10.AH.26.240; 10.AH.26.244; 10.AH.26.243; 10.AH.26.247; 10.AH.27.157; 10.AH.27.158; 10.AH.27.196; 10.AH.27.223; 10.AH.27.240; 10.AH.27.244; 10.AH.27.243; 10.AH.27.247; 10.AH.29.157; 10.AH.29.158; 10.AH.29.196; 10.AH.29.223; 10.AH.29.240; 10.AH.29.244; 10.AH.29.243; 10.AH.29.247; 10.AH.54.157; 10.AH.54.158; 10.AH.54.196; 10.AH.54.223; 10.AH.54.240; 10.AH.54.244; 10.AH.54.243; 10.AH.54.247; 10.AH.55.157; 10.AH.55.158; 10.AH.55.196; 10.AH.55.223; 10.AH.55.240; 10.AH.55.244; 10.AH.55.243; 10.AH.55.247; 10.AH.56.157; 10.AH.56.158;

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Prodrugs of 10.AJ

10.AJ.4.157; 10.AJ.4.158; 10.AJ.4.196; 10.AJ.4.223; 10.AJ.4.240; 10.AJ.4.244; 10.AJ.4.243; 10.AJ.4.247; 10.AJ.5.157; 10.AJ.5.158; 10.AJ.5.196; 10.AJ.5.223; 10.AJ.5.240; 10.AJ.5.244; 10.AJ.5.243; 10.AJ.5.247; 10.AJ.7.157; 10.AJ.7.158; 10.AJ.7.196; 10.AJ.7.223; 10.AJ.7.240; 10.AJ.7.244; 10.AJ.7.243; 10.AJ.7.247; 10.AJ.15.157; 10.AJ.15.158; 10.AJ.15.196; 10.AJ.15.223; 10.AJ.15.240; 10.AJ.15.244; 10.AJ.15.243; 10.AJ.15.247; 10.AJ.16.157; 10.AJ.16.158; 10.AJ.16.196; 10.AJ.16.223; 10.AJ.16.240; 10.AJ.16.244; 10.AJ.16.243; 10.AJ.16.247; 10.AJ.18.157; 10.AJ.18.158; 10.AJ.18.196; 10.AJ.18.223; 10.AJ.18.240; 10.AJ.18.244; 10.AJ.18.243; 10.AJ.18.247; 10.AJ.26.157; 10.AJ.26.158; 10.AJ.26.196; 10.AJ.26.223; 10.AJ.26.240; 10.AJ.26.244; 10.AJ.26.243; 10.AJ.26.247; 10.AJ.27.157; 10.AJ.27.158; 10.AJ.27.196; 10.AJ.27.223; 10.AJ.27.240; 10.AJ.27.244; 10.AJ.27.243; 10.AJ.27.247; 10.AJ.29.157; 10.AJ.29.158; 10.AJ.29.196; 10.AJ.29.223; 10.AJ.29.240; 10.AJ.29.244; 10.AJ.29.243; 10.AJ.29.247; 10.AJ.54.157; 10.AJ.54.158; 10.AJ.54.196; 10.AJ.54.223; 10.AJ.54.240; 10.AJ.54.244; 10.AJ.54.243; 10.AJ.54.247; 10.AJ.55.157; 10.AJ.55.158; 10.AJ.55.196;

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Prodrugs of 10.AN

10.AN.4.157; 10.AN.4.158; 10.AN.4.196; 10.AN.4.223; 10.AN.4.240; 10.AN.4.244; 10.AN.4.243; 10.AN.4.247; 10.AN.5.157; 10.AN.5.158; 10.AN.5.196; 10.AN.5.223; 10.AN.5.240; 10.AN.5.244; 10.AN.5.243; 10.AN.5.247; 10.AN.7.157; 10.AN.7.158; 10.AN.7.196; 10.AN.7.223; 10.AN.7.240; 10.AN.7.244; 10.AN.7.243; 10.AN.7.247; 10.AN.15.157; 10.AN.15.158; 10.AN.15.196; 10.AN.15.223; 10.AN.15.240; 10.AN.15.244; 10.AN.15.243; 10.AN.15.247; 10.AN.16.157; 10.AN.16.158; 10.AN.16.196; 10.AN.16.223; 10.AN.16.240; 10.AN.16.244; 10.AN.16.243; 10.AN.16.247; 10.AN.18.157; 10.AN.18.158; 10.AN.18.196; 10.AN.18.223; 10.AN.18.240; 10.AN.18.244; 10.AN.18.243; 10.AN.18.247; 10.AN.26.157; 10.AN.26.158; 10.AN.26.196; 10.AN.26.223; 10.AN.26.240; 10.AN.26.244; 10.AN.26.243; 10.AN.26.247; 10.AN.27.157; 10.AN.27.158; 10.AN.27.196; 10.AN.27.223; 10.AN.27.240; 10.AN.27.244; 10.AN.27.243; 10.AN.27.247; 10.AN.29.157; 10.AN.29.158; 10.AN.29.196; 10.AN.29.223; 10.AN.29.240; 10.AN.29.244; 10.AN.29.243; 10.AN.29.247; 10.AN.54.157; 10.AN.54.158; 10.AN.54.196; 10.AN.54.223; 10.AN.54.240; 10.AN.54.244; 10.AN.54.243; 10.AN.54.247; 10.AN.55.157; 10.AN.55.158; 10.AN.55.196; 10.AN.55.223; 10.AN.55.240;

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Prodrugs of 10.AP

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Prodrugs of 10.AZ

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Prodrugs of 10.BF

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Prodrugs of 10.CI

10.CI.4.157; 10.CI.4.158; 10.CI.4.196; 10.CI.4.223; 10.CI.4.240; 10.CI.4.244; 10.CI.4.243; 10.CI.4.247; 10.CI.5.157; 10.CI.5.158; 10.CI.5.196; 10.CI.5.223; 10.CI.5.240; 10.CI.5.244; 10.CI.5.243; 10.CI.5.247; 10.CI.7.157; 10.CI.7.158; 10.CI.7.196; 10.CI.7.223; 10.CI.7.240; 10.CI.7.244; 10.CI.7.243; 10.CI.7.247; 10.CI.15.157; 10.CI.15.158; 10.CI.15.196; 10.CI.15.223; 10.CI.15.240; 10.CI.15.244; 10.CI.15.243; 10.CI.15.247; 10.CI.16.157; 10.CI.16.158; 10.CI.16.196; 10.CI.16.223; 10.CI.16.240; 10.CI.16.244; 10.CI.16.243; 10.CI.16.247; 10.CI.18.157; 10.CI.18.158; 10.CI.18.196; 10.CI.18.223; 10.CI.18.240; 10.CI.18.244; 10.CI.18.243; 10.CI.18.247; 10.CI.26.157; 10.CI.26.158; 10.CI.26.196; 10.CI.26.223; 10.CI.26.240; 10.CI.26.244; 10.CI.26.243; 10.CI.26.247; 10.CI.27.157; 10.CI.27.158; 10.CI.27.196; 10.CI.27.223; 10.CI.27.240; 10.CI.27.244; 10.CI.27.243; 10.CI.27.247; 10.CI.29.157; 10.CI.29.158; 10.CI.29.196; 10.CI.29.223; 10.CI.29.240; 10.CI.29.244; 10.CI.29.243; 10.CI.29.247; 10.CI.54.157;

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Prodrugs of 10.CO

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Prodrugs of 11.AH

11.AH.4.157; 11.AH.4.158; 11.AH.4.196; 11.AH.4.223; 11.AH.4.240; 11.AH.4.244; 11.AH.4.243; 11.AH.4.247; 11.AH.5.157; 11.AH.5.158; 11.AH.5.196; 11.AH.5.223; 11.AH.5.240; 11.AH.5.244; 11.AH.5.243; 11.AH.5.247; 11.AH.7.157; 11.AH.7.158; 11.AH.7.196; 11.AH.7.223; 11.AH.7.240; 11.AH.7.244; 11.AH.7.243; 11.AH.7.247; 11.AH.15.157; 11.AH.15.158; 11.AH.15.196; 11.AH.15.223; 11.AH.15.240; 11.AH.15.244; 11.AH.15.243; 11.AH.15.247; 11.AH.16.157; 11.AH.16.158; 11.AH.16.196; 11.AH.16.223; 11.AH.16.240; 11.AH.16.244; 11.AH.16.243; 11.AH.16.247; 11.AH.18.157; 11.AH.18.158; 11.AH.18.196; 11.AH.18.223; 11.AH.18.240; 11.AH.18.244; 11.AH.18.243; 11.AH.18.247; 11.AH.26.157; 11.AH.26.158; 11.AH.26.196; 11.AH.26.223; 11.AH.26.240; 11.AH.26.244; 11.AH.26.243; 11.AH.26.247; 11.AH.27.157; 11.AH.27.158; 11.AH.27.196; 11.AH.27.223; 11.AH.27.240; 11.AH.27.244; 11.AH.27.243; 11.AH.27.247; 11.AH.29.157;

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Prodrugs of 11.AJ

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11.AJ.27.196; 11.AJ.27.223; 11.AJ.27.240; 11.AJ.27.244; 11.AJ.27.243; 11.AJ.27.247; 11.AJ.29.157; 11.AJ.29.158; 11.AJ.29.196; 11.AJ.29.223; 11.AJ.29.240; 11.AJ.29.244; 11.AJ.29.243; 11.AJ.29.247; 11.AJ.54.157; 11.AJ.54.158; 11.AJ.54.196; 11.AJ.54.223; 11.AJ.54.240; 11.AJ.54.244; 11.AJ.54.243; 11.AJ.54.247; 11.AJ.55.157; 11.AJ.55.158; 11.AJ.55.196; 11.AJ.55.223; 11.AJ.55.240; 11.AJ.55.244; 11.AJ.55.243; 11.AJ.55.247; 11.AJ.56.157; 11.AJ.56.158; 11.AJ.56.196; 11.AJ.56.223; 11.AJ.56.240; 11.AJ.56.244; 11.AJ.56.243; 11.AJ.56.247; 11.AJ.157.157; 11.AJ.157.158; 11.AJ.157.196; 11.AJ.157.223; 11.AJ.157.240; 11.AJ.157.244; 11.AJ.157.243; 11.AJ.157.247; 11.AJ.196.157; 11.AJ.196.158; 11.AJ.196.196; 11.AJ.196.223; 11.AJ.196.240; 11.AJ.196.244; 11.AJ.196.243; 11.AJ.196.247; 11.AJ.223.157; 11.AJ.223.158; 11.AJ.223.196; 11.AJ.223.223; 11.AJ.223.240; 11.AJ.223.244; 11.AJ.223.243; 11.AJ.223.247; 11.AJ.240.157; 11.AJ.240.158; 11.AJ.240.196; 11.AJ.240.223; 11.AJ.240.240; 11.AJ.240.244; 11.AJ.240.243; 11.AJ.240.247; 11.AJ.244.157; 11.AJ.244.158; 11.AJ.244.196; 11.AJ.244.223; 11.AJ.244.240; 11.AJ.244.244; 11.AJ.244.243; 11.AJ.244.247; 11.AJ.247.157; 11.AJ.247.158; 11.AJ.247.196; 11.AJ.247.223; 11.AJ.247.240; 11.AJ.247.244; 11.AJ.247.243; 11.AJ.247.247;

Prodrugs of 11.AN

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Prodrugs of 11.AP

11.AP.4.157; 11.AP.4.158; 11.AP.4.196; 11.AP.4.223; 11.AP.4.240; 11.AP.4.244; 11.AP.4.243; 11.AP.4.247; 11.AP.5.157; 11.AP.5.158; 11.AP.5.196; 11.AP.5.223; 11.AP.5.240; 11.AP.5.244; 11.AP.5.243; 11.AP.5.247; 11.AP.7.157; 11.AP.7.158; 11.AP.7.196; 11.AP.7.223; 11.AP.7.240; 11.AP.7.244; 11.AP.7.243; 11.AP.7.247; 11.AP.15.157; 11.AP.15.158; 11.AP.15.196; 11.AP.15.223; 11.AP.15.240; 11.AP.15.244; 11.AP.15.243; 11.AP.15.247; 11.AP.16.157; 11.AP.16.158; 11.AP.16.196; 11.AP.16.223; 11.AP.16.240; 11.AP.16.244; 11.AP.16.243; 11.AP.16.247; 11.AP.18.157; 11.AP.18.158; 11.AP.18.196; 11.AP.18.223; 11.AP.18.240; 11.AP.18.244; 11.AP.18.243; 11.AP.18.247; 11.AP.26.157; 11.AP.26.158;

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Prodrugs of 11.AZ

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Prodrugs of 11.BF

11.BF.4.157; 11.BF.4.158; 11.BF.4.196; 11.BF.4.223; 11.BF.4.240; 11.BF.4.244; 11.BF.4.243; 11.BF.4.247; 11.BF.5.157; 11.BF.5.158; 11.BF.5.196; 11.BF.5.223; 11.BF.5.240; 11.BF.5.244; 11.BF.5.243; 11.BF.5.247; 11.BF.7.157; 11.BF.7.158; 11.BF.7.196; 11.BF.7.223; 11.BF.7.240; 11.BF.7.244; 11.BF.7.243; 11.BF.7.247; 11.BF.15.157; 11.BF.15.158; 11.BF.15.196; 11.BF.15.223; 11.BF.15.240; 11.BF.15.244; 11.BF.15.243; 11.BF.15.247; 11.BF.16.157; 11.BF.16.158; 11.BF.16.196; 11.BF.16.223; 11.BF.16.240; 11.BF.16.244; 11.BF.16.243; 11.BF.16.247;

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Prodrugs of 11.CI

11.CI.4.157; 11.CI.4.158; 11.CI.4.196; 11.CI.4.223; 11.CI.4.240; 11.CI.4.244; 11.CI.4.243; 11.CI.4.247; 11.CI.5.157; 11.CI.5.158; 11.CI.5.196; 11.CI.5.223; 11.CI.5.240; 11.CI.5.244; 11.CI.5.243; 11.CI.5.247; 11.CI.7.157; 11.CI.7.158; 11.CI.7.196; 11.CI.7.223; 11.CI.7.240; 11.CI.7.244; 11.CI.7.243; 11.CI.7.247; 11.CI.15.157; 11.CI.15.158; 11.CI.15.196; 11.CI.15.223; 11.CI.15.240; 11.CI.15.244; 11.CI.15.243; 11.CI.15.247; 11.CI.16.157; 11.CI.16.158; 11.CI.16.196; 11.CI.16.223; 11.CI.16.240; 11.CI.16.244; 11.CI.16.243; 11.CI.16.247; 11.CI.18.157; 11.CI.18.158; 11.CI.18.196; 11.CI.18.223; 11.CI.18.240; 11.CI.18.244; 11.CI.18.243; 11.CI.18.247;

11.CI.26.157; 11.CI.26.158; 11.CI.26.196; 11.CI.26.223; 11.CI.26.240; 11.CI.26.244; 11.CI.26.243; 11.CI.26.247; 11.CI.27.157; 11.CI.27.158; 11.CI.27.196; 11.CI.27.223; 11.CI.27.240; 11.CI.27.244; 11.CI.27.243; 11.CI.27.247; 11.CI.29.157; 11.CI.29.158; 11.CI.29.196; 11.CI.29.223; 11.CI.29.240; 11.CI.29.244; 11.CI.29.243; 11.CI.29.247; 11.CI.54.157; 11.CI.54.158; 11.CI.54.196; 11.CI.54.223; 11.CI.54.240; 11.CI.54.244; 11.CI.54.243; 11.CI.54.247; 11.CI.55.157; 11.CI.55.158; 11.CI.55.196; 11.CI.55.223; 11.CI.55.240; 11.CI.55.244; 11.CI.55.243; 11.CI.55.247; 11.CI.56.157; 11.CI.56.158; 11.CI.56.196; 11.CI.56.223; 11.CI.56.240; 11.CI.56.244; 11.CI.56.243; 11.CI.56.247; 11.CI.157.157; 11.CI.157.158; 11.CI.157.196; 11.CI.157.223; 11.CI.157.240; 11.CI.157.244; 11.CI.157.243; 11.CI.157.247; 11.CI.196.157; 11.CI.196.158; 11.CI.196.196; 11.CI.196.223; 11.CI.196.240; 11.CI.196.244; 11.CI.196.243; 11.CI.196.247; 11.CI.223.157; 11.CI.223.158; 11.CI.223.196; 11.CI.223.223; 11.CI.223.240; 11.CI.223.244; 11.CI.223.243; 11.CI.223.247; 11.CI.240.157; 11.CI.240.158; 11.CI.240.196; 11.CI.240.223; 11.CI.240.240; 11.CI.240.244; 11.CI.240.243; 11.CI.240.247; 11.CI.244.157; 11.CI.244.158; 11.CI.244.196; 11.CI.244.223; 11.CI.244.240; 11.CI.244.244; 11.CI.244.243; 11.CI.244.247; 11.CI.247.157; 11.CI.247.158; 11.CI.247.196; 11.CI.247.223; 11.CI.247.240; 11.CI.247.244; 11.CI.247.243; 11.CI.247.247;

Prodrugs of 11.CO

11.CO.4.157; 11.CO.4.158; 11.CO.4.196; 11.CO.4.223; 11.CO.4.240; 11.CO.4.244; 11.CO.4.243; 11.CO.4.247; 11.CO.5.157; 11.CO.5.158; 11.CO.5.196; 11.CO.5.223; 11.CO.5.240; 11.CO.5.244; 11.CO.5.243; 11.CO.5.247; 11.CO.7.157; 11.CO.7.158; 11.CO.7.196; 11.CO.7.223; 11.CO.7.240; 11.CO.7.244; 11.CO.7.243; 11.CO.7.247; 11.CO.15.157; 11.CO.15.158; 11.CO.15.196; 11.CO.15.223; 11.CO.15.240; 11.CO.15.244; 11.CO.15.243; 11.CO.15.247; 11.CO.16.157; 11.CO.16.158; 11.CO.16.196; 11.CO.16.223; 11.CO.16.240; 11.CO.16.244; 11.CO.16.243; 11.CO.16.247; 11.CO.18.157; 11.CO.18.158; 11.CO.18.196; 11.CO.18.223; 11.CO.18.240; 11.CO.18.244; 11.CO.18.243; 11.CO.18.247; 11.CO.26.157; 11.CO.26.158;

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Prodrugs of 12.AH

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Prodrugs of 12.AJ

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Prodrugs of 12.AP

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Prodrugs of 12.AZ

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Prodrugs of 12.CI

12.CI.4.157; 12.CI.4.158; 12.CI.4.196; 12.CI.4.223; 12.CI.4.240; 12.CI.4.244; 12.CI.4.243; 12.CI.4.247; 12.CI.5.157; 12.CI.5.158; 12.CI.5.196; 12.CI.5.223; 12.CI.5.240; 12.CI.5.244; 12.CI.5.243; 12.CI.5.247; 12.CI.7.157; 12.CI.7.158; 12.CI.7.196; 12.CI.7.223; 12.CI.7.240; 12.CI.7.244; 12.CI.7.243;

12.CI.7.247; 12.CI.15.157; 12.CI.15.158; 12.CI.15.196; 12.CI.15.223; 12.CI.15.240; 12.CI.15.244; 12.CI.15.243; 12.CI.15.247; 12.CI.16.157; 12.CI.16.158; 12.CI.16.196; 12.CI.16.223; 12.CI.16.240; 12.CI.16.244; 12.CI.16.243; 12.CI.16.247; 12.CI.18.157; 12.CI.18.158; 12.CI.18.196; 12.CI.18.223; 12.CI.18.240; 12.CI.18.244; 12.CI.18.243; 12.CI.18.247; 12.CI.26.157; 12.CI.26.158; 12.CI.26.196; 12.CI.26.223; 12.CI.26.240; 12.CI.26.244; 12.CI.26.243; 12.CI.26.247; 12.CI.27.157; 12.CI.27.158; 12.CI.27.196; 12.CI.27.223; 12.CI.27.240; 12.CI.27.244; 12.CI.27.243; 12.CI.27.247; 12.CI.29.157; 12.CI.29.158; 12.CI.29.196; 12.CI.29.223; 12.CI.29.240; 12.CI.29.244; 12.CI.29.243; 12.CI.29.247; 12.CI.54.157; 12.CI.54.158; 12.CI.54.196; 12.CI.54.223; 12.CI.54.240; 12.CI.54.244; 12.CI.54.243; 12.CI.54.247; 12.CI.55.157; 12.CI.55.158; 12.CI.55.196; 12.CI.55.223; 12.CI.55.240; 12.CI.55.244; 12.CI.55.243; 12.CI.55.247; 12.CI.56.157; 12.CI.56.158; 12.CI.56.196; 12.CI.56.223; 12.CI.56.240; 12.CI.56.244; 12.CI.56.243; 12.CI.56.247; 12.CI.157.157; 12.CI.157.158; 12.CI.157.196; 12.CI.157.223; 12.CI.157.240; 12.CI.157.244; 12.CI.157.243; 12.CI.157.247; 12.CI.196.157; 12.CI.196.158; 12.CI.196.196; 12.CI.196.223; 12.CI.196.240; 12.CI.196.244; 12.CI.196.243; 12.CI.196.247; 12.CI.223.157; 12.CI.223.158; 12.CI.223.196; 12.CI.223.223; 12.CI.223.240; 12.CI.223.244; 12.CI.223.243; 12.CI.223.247; 12.CI.240.157; 12.CI.240.158; 12.CI.240.196; 12.CI.240.223; 12.CI.240.240; 12.CI.240.244; 12.CI.240.243; 12.CI.240.247; 12.CI.244.157; 12.CI.244.158; 12.CI.244.196; 12.CI.244.223; 12.CI.244.240; 12.CI.244.244; 12.CI.244.243; 12.CI.244.247; 12.CI.247.157; 12.CI.247.158; 12.CI.247.196; 12.CI.247.223; 12.CI.247.240; 12.CI.247.244; 12.CI.247.243; 12.CI.247.247;

Prodrugs of 12.CO

12.CO.4.157; 12.CO.4.158; 12.CO.4.196; 12.CO.4.223; 12.CO.4.240; 12.CO.4.244; 12.CO.4.243; 12.CO.4.247; 12.CO.5.157; 12.CO.5.158; 12.CO.5.196; 12.CO.5.223; 12.CO.5.240; 12.CO.5.244; 12.CO.5.243; 12.CO.5.247; 12.CO.7.157; 12.CO.7.158; 12.CO.7.196; 12.CO.7.223; 12.CO.7.240; 12.CO.7.244; 12.CO.7.243; 12.CO.7.247; 12.CO.15.157;

12.CO.15.158; 12.CO.15.196; 12.CO.15.223; 12.CO.15.240; 12.CO.15.244; 12.CO.15.243; 12.CO.15.247; 12.CO.16.157; 12.CO.16.158; 12.CO.16.196; 12.CO.16.223; 12.CO.16.240; 12.CO.16.244; 12.CO.16.243; 12.CO.16.247; 12.CO.18.157; 12.CO.18.158; 12.CO.18.196; 12.CO.18.223; 12.CO.18.240; 12.CO.18.244; 12.CO.18.243; 12.CO.18.247; 12.CO.26.157; 12.CO.26.158; 12.CO.26.196; 12.CO.26.223; 12.CO.26.240; 12.CO.26.244; 12.CO.26.243; 12.CO.26.247; 12.CO.27.157; 12.CO.27.158; 12.CO.27.196; 12.CO.27.223; 12.CO.27.240; 12.CO.27.244; 12.CO.27.243; 12.CO.27.247; 12.CO.29.157; 12.CO.29.158; 12.CO.29.196; 12.CO.29.223; 12.CO.29.240; 12.CO.29.244; 12.CO.29.243; 12.CO.29.247; 12.CO.54.157; 12.CO.54.158; 12.CO.54.196; 12.CO.54.223; 12.CO.54.240; 12.CO.54.244; 12.CO.54.243; 12.CO.54.247; 12.CO.55.157; 12.CO.55.158; 12.CO.55.196; 12.CO.55.223; 12.CO.55.240; 12.CO.55.244; 12.CO.55.243; 12.CO.55.247; 12.CO.56.157; 12.CO.56.158; 12.CO.56.196; 12.CO.56.223; 12.CO.56.240; 12.CO.56.244; 12.CO.56.243; 12.CO.56.247; 12.CO.157.157; 12.CO.157.158; 12.CO.157.196; 12.CO.157.223; 12.CO.157.240; 12.CO.157.244; 12.CO.157.243; 12.CO.157.247; 12.CO.196.157; 12.CO.196.158; 12.CO.196.196; 12.CO.196.223; 12.CO.196.240; 12.CO.196.244; 12.CO.196.243; 12.CO.196.247; 12.CO.223.157; 12.CO.223.158; 12.CO.223.196; 12.CO.223.223; 12.CO.223.240; 12.CO.223.244; 12.CO.223.243; 12.CO.223.247; 12.CO.240.157; 12.CO.240.158; 12.CO.240.196; 12.CO.240.223; 12.CO.240.240; 12.CO.240.244; 12.CO.240.243; 12.CO.240.247; 12.CO.244.157; 12.CO.244.158; 12.CO.244.196; 12.CO.244.223; 12.CO.244.240; 12.CO.244.244; 12.CO.244.243; 12.CO.244.247; 12.CO.247.157; 12.CO.247.158; 12.CO.247.196; 12.CO.247.223; 12.CO.247.240; 12.CO.247.244; 12.CO.247.243; 12.CO.247.247.

Prodrugs of 13.B

13.B.228.228; 13.B.228.229; 13.B.228.230; 13.B.228.231; 13.B.228.236; 13.B.228.237; 13.B.228.238; 13.B.228.239; 13.B.228.154; 13.B.228.157; 13.B.228.166; 13.B.228.169; 13.B.228.172; 13.B.228.175; 13.B.228.240; 13.B.228.244; 13.B.229.228; 13.B.229.229; 13.B.229.230; 13.B.229.231; 13.B.229.236; 13.B.229.237; 13.B.229.238; 13.B.229.239; 13.B.229.154; 13.B.229.157; 13.B.229.166; 13.B.229.169; 13.B.229.172; 13.B.229.175; 13.B.229.240; 13.B.229.244; 13.B.230.228; 13.B.230.229; 13.B.230.230; 13.B.230.231; 13.B.230.236; 13.B.230.237; 13.B.230.238; 13.B.230.239; 13.B.230.154; 13.B.230.157; 13.B.230.166; 13.B.230.169; 13.B.230.172; 13.B.230.175; 13.B.230.240; 13.B.230.244; 13.B.231.228; 13.B.231.229; 13.B.231.230; 13.B.231.231; 13.B.231.236; 13.B.231.237; 13.B.231.238; 13.B.231.239; 13.B.231.154; 13.B.231.157; 13.B.231.166; 13.B.231.169; 13.B.231.172; 13.B.231.175; 13.B.231.240; 13.B.231.244; 13.B.236.228; 13.B.236.229; 13.B.236.230; 13.B.236.231; 13.B.236.236; 13.B.236.237; 13.B.236.238; 13.B.236.239; 13.B.236.154; 13.B.236.157; 13.B.236.166; 13.B.236.169; 13.B.236.172; 13.B.236.175; 13.B.236.240; 13.B.236.244; 13.B.237.228; 13.B.237.229; 13.B.237.230; 13.B.237.231; 13.B.237.236; 13.B.237.237; 13.B.237.238; 13.B.237.239; 13.B.237.154; 13.B.237.157; 13.B.237.166; 13.B.237.169; 13.B.237.172; 13.B.237.175; 13.B.237.240; 13.B.237.244; 13.B.238.228; 13.B.238.229; 13.B.238.230; 13.B.238.231; 13.B.238.236; 13.B.238.237; 13.B.238.238; 13.B.238.239; 13.B.238.154; 13.B.238.157; 13.B.238.166; 13.B.238.169; 13.B.238.172; 13.B.238.175; 13.B.238.240; 13.B.238.244; 13.B.239.228; 13.B.239.229; 13.B.239.230; 13.B.239.231; 13.B.239.236; 13.B.239.237; 13.B.239.238; 13.B.239.239; 13.B.239.154; 13.B.239.157; 13.B.239.166; 13.B.239.169; 13.B.239.172; 13.B.239.175; 13.B.239.240; 13.B.239.244; 13.B.154.228; 13.B.154.229; 13.B.154.230; 13.B.154.231; 13.B.154.236; 13.B.154.237; 13.B.154.238; 13.B.154.239; 13.B.154.154; 13.B.154.157; 13.B.154.166; 13.B.154.169;

13.B.154.172; 13.B.154.175; 13.B.154.240; 13.B.154.244; 13.B.157.228; 13.B.157.229; 13.B.157.230; 13.B.157.231; 13.B.157.236; 13.B.157.237; 13.B.157.238; 13.B.157.239; 13.B.157.154; 13.B.157.157; 13.B.157.166; 13.B.157.169; 13.B.157.172; 13.B.157.175; 13.B.157.240; 13.B.157.244; 13.B.166.228; 13.B.166.229; 13.B.166.230; 13.B.166.231; 13.B.166.236; 13.B.166.237; 13.B.166.238; 13.B.166.239; 13.B.166.154; 13.B.166.157; 13.B.166.166; 13.B.166.169; 13.B.166.172; 13.B.166.175; 13.B.166.240; 13.B.166.244; 13.B.169.228; 13.B.169.229; 13.B.169.230; 13.B.169.231; 13.B.169.236; 13.B.169.237; 13.B.169.238; 13.B.169.239; 13.B.169.154; 13.B.169.157; 13.B.169.166; 13.B.169.169; 13.B.169.172; 13.B.169.175; 13.B.169.240; 13.B.169.244; 13.B.172.228; 13.B.172.229; 13.B.172.230; 13.B.172.231; 13.B.172.236; 13.B.172.237; 13.B.172.238; 13.B.172.239; 13.B.172.154; 13.B.172.157; 13.B.172.166; 13.B.172.169; 13.B.172.172; 13.B.172.175; 13.B.172.240; 13.B.172.244; 13.B.175.228; 13.B.175.229; 13.B.175.230; 13.B.175.231; 13.B.175.236; 13.B.175.237; 13.B.175.238; 13.B.175.239; 13.B.175.154; 13.B.175.157; 13.B.175.166; 13.B.175.169; 13.B.175.172; 13.B.175.175; 13.B.175.240; 13.B.175.244; 13.B.240.228; 13.B.240.229; 13.B.240.230; 13.B.240.231; 13.B.240.236; 13.B.240.237; 13.B.240.238; 13.B.240.239; 13.B.240.154; 13.B.240.157; 13.B.240.166; 13.B.240.169; 13.B.240.172; 13.B.240.175; 13.B.240.240; 13.B.240.244; 13.B.244.228; 13.B.244.229; 13.B.244.230; 13.B.244.231; 13.B.244.236; 13.B.244.237; 13.B.244.238; 13.B.244.239; 13.B.244.154; 13.B.244.157; 13.B.244.166; 13.B.244.169; 13.B.244.172; 13.B.244.175; 13.B.244.240; 13.B.244.244;

Prodrugs of 13.D

13.D.228.228; 13.D.228.229; 13.D.228.230; 13.D.228.231; 13.D.228.236; 13.D.228.237; 13.D.228.238; 13.D.228.239; 13.D.228.154; 13.D.228.157; 13.D.228.166; 13.D.228.169; 13.D.228.172; 13.D.228.175; 13.D.228.240; 13.D.228.244; 13.D.229.228; 13.D.229.229; 13.D.229.230; 13.D.229.231;

13.D.229.236; 13.D.229.237; 13.D.229.238; 13.D.229.239; 13.D.229.154; 13.D.229.157; 13.D.229.166; 13.D.229.169; 13.D.229.172; 13.D.229.175; 13.D.229.240; 13.D.229.244; 13.D.230.228; 13.D.230.229; 13.D.230.230; 13.D.230.231; 13.D.230.236; 13.D.230.237; 13.D.230.238; 13.D.230.239; 13.D.230.154; 13.D.230.157; 13.D.230.166; 13.D.230.169; 13.D.230.172; 13.D.230.175; 13.D.230.240; 13.D.230.244; 13.D.231.228; 13.D.231.229; 13.D.231.230; 13.D.231.231; 13.D.231.236; 13.D.231.237; 13.D.231.238; 13.D.231.239; 13.D.231.154; 13.D.231.157; 13.D.231.166; 13.D.231.169; 13.D.231.172; 13.D.231.175; 13.D.231.240; 13.D.231.244; 13.D.236.228; 13.D.236.229; 13.D.236.230; 13.D.236.231; 13.D.236.236; 13.D.236.237; 13.D.236.238; 13.D.236.239; 13.D.236.154; 13.D.236.157; 13.D.236.166; 13.D.236.169; 13.D.236.172; 13.D.236.175; 13.D.236.240; 13.D.236.244; 13.D.237.228; 13.D.237.229; 13.D.237.230; 13.D.237.231; 13.D.237.236; 13.D.237.237; 13.D.237.238; 13.D.237.239; 13.D.237.154; 13.D.237.157; 13.D.237.166; 13.D.237.169; 13.D.237.172; 13.D.237.175; 13.D.237.240; 13.D.237.244; 13.D.238.228; 13.D.238.229; 13.D.238.230; 13.D.238.231; 13.D.238.236; 13.D.238.237; 13.D.238.238; 13.D.238.239; 13.D.238.154; 13.D.238.157; 13.D.238.166; 13.D.238.169; 13.D.238.172; 13.D.238.175; 13.D.238.240; 13.D.238.244; 13.D.239.228; 13.D.239.229; 13.D.239.230; 13.D.239.231; 13.D.239.236; 13.D.239.237; 13.D.239.238; 13.D.239.239; 13.D.239.154; 13.D.239.157; 13.D.239.166; 13.D.239.169; 13.D.239.172; 13.D.239.175; 13.D.239.240; 13.D.239.244; 13.D.154.228; 13.D.154.229; 13.D.154.230; 13.D.154.231; 13.D.154.236; 13.D.154.237; 13.D.154.238; 13.D.154.239; 13.D.154.154; 13.D.154.157; 13.D.154.166; 13.D.154.169; 13.D.154.172; 13.D.154.175; 13.D.154.240; 13.D.154.244; 13.D.157.228; 13.D.157.229; 13.D.157.230; 13.D.157.231; 13.D.157.236; 13.D.157.237; 13.D.157.238; 13.D.157.239; 13.D.157.154; 13.D.157.157; 13.D.157.166; 13.D.157.169; 13.D.157.172; 13.D.157.175; 13.D.157.240; 13.D.157.244; 13.D.166.228; 13.D.166.229; 13.D.166.230; 13.D.166.231; 13.D.166.236; 13.D.166.237; 13.D.166.238; 13.D.166.239; 13.D.166.154; 13.D.166.157;

13.D.166.166; 13.D.166.169; 13.D.166.172; 13.D.166.175; 13.D.166.240; 13.D.166.244; 13.D.169.228; 13.D.169.229; 13.D.169.230; 13.D.169.231; 13.D.169.236; 13.D.169.237; 13.D.169.238; 13.D.169.239; 13.D.169.154; 13.D.169.157; 13.D.169.166; 13.D.169.169; 13.D.169.172; 13.D.169.175; 13.D.169.240; 13.D.169.244; 13.D.172.228; 13.D.172.229; 13.D.172.230; 13.D.172.231; 13.D.172.236; 13.D.172.237; 13.D.172.238; 13.D.172.239; 13.D.172.154; 13.D.172.157; 13.D.172.166; 13.D.172.169; 13.D.172.172; 13.D.172.175; 13.D.172.240; 13.D.172.244; 13.D.175.228; 13.D.175.229; 13.D.175.230; 13.D.175.231; 13.D.175.236; 13.D.175.237; 13.D.175.238; 13.D.175.239; 13.D.175.154; 13.D.175.157; 13.D.175.166; 13.D.175.169; 13.D.175.172; 13.D.175.175; 13.D.175.240; 13.D.175.244; 13.D.240.228; 13.D.240.229; 13.D.240.230; 13.D.240.231; 13.D.240.236; 13.D.240.237; 13.D.240.238; 13.D.240.239; 13.D.240.154; 13.D.240.157; 13.D.240.166; 13.D.240.169; 13.D.240.172; 13.D.240.175; 13.D.240.240; 13.D.240.244; 13.D.244.228; 13.D.244.229; 13.D.244.230; 13.D.244.231; 13.D.244.236; 13.D.244.237; 13.D.244.238; 13.D.244.239; 13.D.244.154; 13.D.244.157; 13.D.244.166; 13.D.244.169; 13.D.244.172; 13.D.244.175; 13.D.244.240; 13.D.244.244;

Prodrugs of 13.E

13.E.228.228; 13.E.228.229; 13.E.228.230; 13.E.228.231; 13.E.228.236; 13.E.228.237; 13.E.228.238; 13.E.228.239; 13.E.228.154; 13.E.228.157; 13.E.228.166; 13.E.228.169; 13.E.228.172; 13.E.228.175; 13.E.228.240; 13.E.228.244; 13.E.229.228; 13.E.229.229; 13.E.229.230; 13.E.229.231; 13.E.229.236; 13.E.229.237; 13.E.229.238; 13.E.229.239; 13.E.229.154; 13.E.229.157; 13.E.229.166; 13.E.229.169; 13.E.229.172; 13.E.229.175; 13.E.229.240; 13.E.229.244; 13.E.230.228; 13.E.230.229; 13.E.230.230; 13.E.230.231; 13.E.230.236; 13.E.230.237; 13.E.230.238; 13.E.230.239; 13.E.230.154; 13.E.230.157; 13.E.230.166; 13.E.230.169; 13.E.230.172; 13.E.230.175; 13.E.230.240; 13.E.230.244; 13.E.231.228; 13.E.231.229;

13.E.231.230; 13.E.231.231; 13.E.231.236; 13.E.231.237; 13.E.231.238; 13.E.231.239; 13.E.231.154; 13.E.231.157; 13.E.231.166; 13.E.231.169; 13.E.231.172; 13.E.231.175; 13.E.231.240; 13.E.231.244; 13.E.236.228; 13.E.236.229; 13.E.236.230; 13.E.236.231; 13.E.236.236; 13.E.236.237; 13.E.236.238; 13.E.236.239; 13.E.236.154; 13.E.236.157; 13.E.236.166; 13.E.236.169; 13.E.236.172; 13.E.236.175; 13.E.236.240; 13.E.236.244; 13.E.237.228; 13.E.237.229; 13.E.237.230; 13.E.237.231; 13.E.237.236; 13.E.237.237; 13.E.237.238; 13.E.237.239; 13.E.237.154; 13.E.237.157; 13.E.237.166; 13.E.237.169; 13.E.237.172; 13.E.237.175; 13.E.237.240; 13.E.237.244; 13.E.238.228; 13.E.238.229; 13.E.238.230; 13.E.238.231; 13.E.238.236; 13.E.238.237; 13.E.238.238; 13.E.238.239; 13.E.238.154; 13.E.238.157; 13.E.238.166; 13.E.238.169; 13.E.238.172; 13.E.238.175; 13.E.238.240; 13.E.238.244; 13.E.239.228; 13.E.239.229; 13.E.239.230; 13.E.239.231; 13.E.239.236; 13.E.239.237; 13.E.239.238; 13.E.239.239; 13.E.239.154; 13.E.239.157; 13.E.239.166; 13.E.239.169; 13.E.239.172; 13.E.239.175; 13.E.239.240; 13.E.239.244; 13.E.154.228; 13.E.154.229; 13.E.154.230; 13.E.154.231; 13.E.154.236; 13.E.154.237; 13.E.154.238; 13.E.154.239; 13.E.154.154; 13.E.154.157; 13.E.154.166; 13.E.154.169; 13.E.154.172; 13.E.154.175; 13.E.154.240; 13.E.154.244; 13.E.157.228; 13.E.157.229; 13.E.157.230; 13.E.157.231; 13.E.157.236; 13.E.157.237; 13.E.157.238; 13.E.157.239; 13.E.157.154; 13.E.157.157; 13.E.157.166; 13.E.157.169; 13.E.157.172; 13.E.157.175; 13.E.157.240; 13.E.157.244; 13.E.166.228; 13.E.166.229; 13.E.166.230; 13.E.166.231; 13.E.166.236; 13.E.166.237; 13.E.166.238; 13.E.166.239; 13.E.166.154; 13.E.166.157; 13.E.166.166; 13.E.166.169; 13.E.166.172; 13.E.166.175; 13.E.166.240; 13.E.166.244; 13.E.169.228; 13.E.169.229; 13.E.169.230; 13.E.169.231; 13.E.169.236; 13.E.169.237; 13.E.169.238; 13.E.169.239; 13.E.169.154; 13.E.169.157; 13.E.169.166; 13.E.169.169; 13.E.169.172; 13.E.169.175; 13.E.169.240; 13.E.169.244; 13.E.172.228; 13.E.172.229; 13.E.172.230; 13.E.172.231; 13.E.172.236; 13.E.172.237; 13.E.172.238; 13.E.172.239;

13.E.172.154; 13.E.172.157; 13.E.172.166; 13.E.172.169; 13.E.172.172; 13.E.172.175; 13.E.172.240; 13.E.172.244; 13.E.175.228; 13.E.175.229; 13.E.175.230; 13.E.175.231; 13.E.175.236; 13.E.175.237; 13.E.175.238; 13.E.175.239; 13.E.175.154; 13.E.175.157; 13.E.175.166; 13.E.175.169; 13.E.175.172; 13.E.175.175; 13.E.175.240; 13.E.175.244; 13.E.240.228; 13.E.240.229; 13.E.240.230; 13.E.240.231; 13.E.240.236; 13.E.240.237; 13.E.240.238; 13.E.240.239; 13.E.240.154; 13.E.240.157; 13.E.240.166; 13.E.240.169; 13.E.240.172; 13.E.240.175; 13.E.240.240; 13.E.240.244; 13.E.244.228; 13.E.244.229; 13.E.244.230; 13.E.244.231; 13.E.244.236; 13.E.244.237; 13.E.244.238; 13.E.244.239; 13.E.244.154; 13.E.244.157; 13.E.244.166; 13.E.244.169; 13.E.244.172; 13.E.244.175; 13.E.244.240; 13.E.244.244;

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13.G.240.238; 13.G.240.239; 13.G.240.154; 13.G.240.157; 13.G.240.166; 13.G.240.169; 13.G.240.172; 13.G.240.175; 13.G.240.240; 13.G.240.244; 13.G.244.228; 13.G.244.229; 13.G.244.230; 13.G.244.231; 13.G.244.236; 13.G.244.237; 13.G.244.238; 13.G.244.239; 13.G.244.154; 13.G.244.157; 13.G.244.166; 13.G.244.169; 13.G.244.172; 13.G.244.175; 13.G.244.240; 13.G.244.244;

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13.I.238.240; 13.I.238.244; 13.I.239.228; 13.I.239.229; 13.I.239.230; 13.I.239.231; 13.I.239.236; 13.I.239.237; 13.I.239.238; 13.I.239.239; 13.I.239.154; 13.I.239.157; 13.I.239.166; 13.I.239.169; 13.I.239.172; 13.I.239.175; 13.I.239.240; 13.I.239.244; 13.I.154.228; 13.I.154.229; 13.I.154.230; 13.I.154.231; 13.I.154.236; 13.I.154.237; 13.I.154.238; 13.I.154.239; 13.I.154.154; 13.I.154.157; 13.I.154.166; 13.I.154.169; 13.I.154.172; 13.I.154.175; 13.I.154.240; 13.I.154.244; 13.I.157.228; 13.I.157.229; 13.I.157.230; 13.I.157.231; 13.I.157.236; 13.I.157.237; 13.I.157.238; 13.I.157.239; 13.I.157.154; 13.I.157.157; 13.I.157.166; 13.I.157.169; 13.I.157.172; 13.I.157.175; 13.I.157.240; 13.I.157.244; 13.I.166.228; 13.I.166.229; 13.I.166.230; 13.I.166.231; 13.I.166.236; 13.I.166.237; 13.I.166.238; 13.I.166.239; 13.I.166.154; 13.I.166.157; 13.I.166.166; 13.I.166.169; 13.I.166.172; 13.I.166.175; 13.I.166.240; 13.I.166.244; 13.I.169.228; 13.I.169.229; 13.I.169.230; 13.I.169.231; 13.I.169.236; 13.I.169.237; 13.I.169.238; 13.I.169.239; 13.I.169.154; 13.I.169.157; 13.I.169.166; 13.I.169.169; 13.I.169.172; 13.I.169.175; 13.I.169.240; 13.I.169.244; 13.I.172.228; 13.I.172.229; 13.I.172.230; 13.I.172.231; 13.I.172.236; 13.I.172.237; 13.I.172.238; 13.I.172.239; 13.I.172.154; 13.I.172.157; 13.I.172.166; 13.I.172.169; 13.I.172.172; 13.I.172.175; 13.I.172.240; 13.I.172.244; 13.I.175.228; 13.I.175.229; 13.I.175.230; 13.I.175.231; 13.I.175.236; 13.I.175.237; 13.I.175.238; 13.I.175.239; 13.I.175.154; 13.I.175.157; 13.I.175.166; 13.I.175.169; 13.I.175.172; 13.I.175.175; 13.I.175.240; 13.I.175.244; 13.I.240.228; 13.I.240.229; 13.I.240.230; 13.I.240.231; 13.I.240.236; 13.I.240.237; 13.I.240.238; 13.I.240.239; 13.I.240.154; 13.I.240.157; 13.I.240.166; 13.I.240.169; 13.I.240.172; 13.I.240.175; 13.I.240.240; 13.I.240.244; 13.I.244.228; 13.I.244.229; 13.I.244.230; 13.I.244.231; 13.I.244.236; 13.I.244.237; 13.I.244.238; 13.I.244.239; 13.I.244.154; 13.I.244.157; 13.I.244.166; 13.I.244.169; 13.I.244.172; 13.I.244.175; 13.I.244.240; 13.I.244.244;

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13.J.228.228; 13.J.228.229; 13.J.228.230; 13.J.228.231; 13.J.228.236; 13.J.228.237; 13.J.228.238; 13.J.228.239; 13.J.228.154; 13.J.228.157; 13.J.228.166; 13.J.228.169; 13.J.228.172; 13.J.228.175; 13.J.228.240; 13.J.228.244; 13.J.229.228; 13.J.229.229; 13.J.229.230; 13.J.229.231; 13.J.229.236; 13.J.229.237; 13.J.229.238; 13.J.229.239; 13.J.229.154; 13.J.229.157; 13.J.229.166; 13.J.229.169; 13.J.229.172; 13.J.229.175; 13.J.229.240; 13.J.229.244; 13.J.230.228; 13.J.230.229; 13.J.230.230; 13.J.230.231; 13.J.230.236; 13.J.230.237; 13.J.230.238; 13.J.230.239; 13.J.230.154; 13.J.230.157; 13.J.230.166; 13.J.230.169; 13.J.230.172; 13.J.230.175; 13.J.230.240; 13.J.230.244; 13.J.231.228; 13.J.231.229; 13.J.231.230; 13.J.231.231; 13.J.231.236; 13.J.231.237; 13.J.231.238; 13.J.231.239; 13.J.231.154; 13.J.231.157; 13.J.231.166; 13.J.231.169; 13.J.231.172; 13.J.231.175; 13.J.231.240; 13.J.231.244; 13.J.236.228; 13.J.236.229; 13.J.236.230; 13.J.236.231; 13.J.236.236; 13.J.236.237; 13.J.236.238; 13.J.236.239; 13.J.236.154; 13.J.236.157; 13.J.236.166; 13.J.236.169; 13.J.236.172; 13.J.236.175; 13.J.236.240; 13.J.236.244; 13.J.237.228; 13.J.237.229; 13.J.237.230; 13.J.237.231; 13.J.237.236; 13.J.237.237; 13.J.237.238; 13.J.237.239; 13.J.237.154; 13.J.237.157; 13.J.237.166; 13.J.237.169; 13.J.237.172; 13.J.237.175; 13.J.237.240; 13.J.237.244; 13.J.238.228; 13.J.238.229; 13.J.238.230; 13.J.238.231; 13.J.238.236; 13.J.238.237; 13.J.238.238; 13.J.238.239; 13.J.238.154; 13.J.238.157; 13.J.238.166; 13.J.238.169; 13.J.238.172; 13.J.238.175; 13.J.238.240; 13.J.238.244; 13.J.239.228; 13.J.239.229; 13.J.239.230; 13.J.239.231; 13.J.239.236; 13.J.239.237; 13.J.239.238; 13.J.239.239; 13.J.239.154; 13.J.239.157; 13.J.239.166; 13.J.239.169; 13.J.239.172; 13.J.239.175; 13.J.239.240; 13.J.239.244; 13.J.154.228; 13.J.154.229; 13.J.154.230; 13.J.154.231; 13.J.154.236; 13.J.154.237; 13.J.154.238; 13.J.154.239; 13.J.154.154; 13.J.154.157; 13.J.154.166; 13.J.154.169;

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Prodrugs of 13.U

13.U.228.228; 13.U.228.229; 13.U.228.230; 13.U.228.231; 13.U.228.236; 13.U.228.237; 13.U.228.238; 13.U.228.239; 13.U.228.154; 13.U.228.157; 13.U.228.166; 13.U.228.169; 13.U.228.172; 13.U.228.175; 13.U.228.240; 13.U.228.244; 13.U.229.228; 13.U.229.229; 13.U.229.230; 13.U.229.231; 13.U.229.236; 13.U.229.237; 13.U.229.238; 13.U.229.239; 13.U.229.154; 13.U.229.157; 13.U.229.166; 13.U.229.169; 13.U.229.172; 13.U.229.175; 13.U.229.240; 13.U.229.244; 13.U.230.228; 13.U.230.229; 13.U.230.230; 13.U.230.231; 13.U.230.236; 13.U.230.237; 13.U.230.238; 13.U.230.239; 13.U.230.154; 13.U.230.157; 13.U.230.166; 13.U.230.169; 13.U.230.172; 13.U.230.175; 13.U.230.240; 13.U.230.244; 13.U.231.228; 13.U.231.229; 13.U.231.230; 13.U.231.231; 13.U.231.236; 13.U.231.237; 13.U.231.238; 13.U.231.239; 13.U.231.154; 13.U.231.157; 13.U.231.166; 13.U.231.169; 13.U.231.172; 13.U.231.175; 13.U.231.240; 13.U.231.244; 13.U.236.228; 13.U.236.229; 13.U.236.230; 13.U.236.231; 13.U.236.236; 13.U.236.237; 13.U.236.238; 13.U.236.239; 13.U.236.154; 13.U.236.157; 13.U.236.166; 13.U.236.169; 13.U.236.172; 13.U.236.175; 13.U.236.240; 13.U.236.244; 13.U.237.228; 13.U.237.229; 13.U.237.230; 13.U.237.231; 13.U.237.236; 13.U.237.237; 13.U.237.238; 13.U.237.239; 13.U.237.154; 13.U.237.157; 13.U.237.166; 13.U.237.169; 13.U.237.172; 13.U.237.175; 13.U.237.240; 13.U.237.244; 13.U.238.228; 13.U.238.229; 13.U.238.230; 13.U.238.231; 13.U.238.236; 13.U.238.237; 13.U.238.238; 13.U.238.239; 13.U.238.154; 13.U.238.157; 13.U.238.166; 13.U.238.169; 13.U.238.172; 13.U.238.175;

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Prodrugs of 13.W

13.W.228.228; 13.W.228.229; 13.W.228.230; 13.W.228.231; 13.W.228.236; 13.W.228.237; 13.W.228.238; 13.W.228.239; 13.W.228.154; 13.W.228.157; 13.W.228.166; 13.W.228.169; 13.W.228.172; 13.W.228.175; 13.W.228.240; 13.W.228.244; 13.W.229.228; 13.W.229.229; 13.W.229.230; 13.W.229.231; 13.W.229.236; 13.W.229.237; 13.W.229.238; 13.W.229.239; 13.W.229.154; 13.W.229.157; 13.W.229.166; 13.W.229.169; 13.W.229.172; 13.W.229.175; 13.W.229.240; 13.W.229.244; 13.W.230.228; 13.W.230.229; 13.W.230.230; 13.W.230.231; 13.W.230.236; 13.W.230.237; 13.W.230.238; 13.W.230.239; 13.W.230.154; 13.W.230.157; 13.W.230.166; 13.W.230.169; 13.W.230.172; 13.W.230.175; 13.W.230.240; 13.W.230.244; 13.W.231.228; 13.W.231.229; 13.W.231.230; 13.W.231.231; 13.W.231.236; 13.W.231.237; 13.W.231.238; 13.W.231.239; 13.W.231.154; 13.W.231.157; 13.W.231.166; 13.W.231.169; 13.W.231.172; 13.W.231.175; 13.W.231.240; 13.W.231.244; 13.W.236.228; 13.W.236.229; 13.W.236.230; 13.W.236.231; 13.W.236.236; 13.W.236.237; 13.W.236.238; 13.W.236.239; 13.W.236.154; 13.W.236.157; 13.W.236.166; 13.W.236.169; 13.W.236.172; 13.W.236.175; 13.W.236.240; 13.W.236.244; 13.W.237.228; 13.W.237.229; 13.W.237.230; 13.W.237.231; 13.W.237.236; 13.W.237.237; 13.W.237.238; 13.W.237.239; 13.W.237.154; 13.W.237.157; 13.W.237.166; 13.W.237.169; 13.W.237.172; 13.W.237.175; 13.W.237.240; 13.W.237.244; 13.W.238.228; 13.W.238.229; 13.W.238.230; 13.W.238.231; 13.W.238.236; 13.W.238.237; 13.W.238.238; 13.W.238.239; 13.W.238.154; 13.W.238.157; 13.W.238.166; 13.W.238.169; 13.W.238.172; 13.W.238.175; 13.W.238.240; 13.W.238.244; 13.W.239.228; 13.W.239.229; 13.W.239.230; 13.W.239.231; 13.W.239.236; 13.W.239.237; 13.W.239.238; 13.W.239.239; 13.W.239.154; 13.W.239.157; 13.W.239.166; 13.W.239.169; 13.W.239.172; 13.W.239.175; 13.W.239.240; 13.W.239.244; 13.W.154.228; 13.W.154.229; 13.W.154.230; 13.W.154.231; 13.W.154.236; 13.W.154.237; 13.W.154.238; 13.W.154.239; 13.W.154.154; 13.W.154.157; 13.W.154.166; 13.W.154.169;

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Prodrugs of 13.Y

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13.Y.166.166; 13.Y.166.169; 13.Y.166.172; 13.Y.166.175; 13.Y.166.240; 13.Y.166.244; 13.Y.169.228; 13.Y.169.229; 13.Y.169.230; 13.Y.169.231; 13.Y.169.236; 13.Y.169.237; 13.Y.169.238; 13.Y.169.239; 13.Y.169.154; 13.Y.169.157; 13.Y.169.166; 13.Y.169.169; 13.Y.169.172; 13.Y.169.175; 13.Y.169.240; 13.Y.169.244; 13.Y.172.228; 13.Y.172.229; 13.Y.172.230; 13.Y.172.231; 13.Y.172.236; 13.Y.172.237; 13.Y.172.238; 13.Y.172.239; 13.Y.172.154; 13.Y.172.157; 13.Y.172.166; 13.Y.172.169; 13.Y.172.172; 13.Y.172.175; 13.Y.172.240; 13.Y.172.244; 13.Y.175.228; 13.Y.175.229; 13.Y.175.230; 13.Y.175.231; 13.Y.175.236; 13.Y.175.237; 13.Y.175.238; 13.Y.175.239; 13.Y.175.154; 13.Y.175.157; 13.Y.175.166; 13.Y.175.169; 13.Y.175.172; 13.Y.175.175; 13.Y.175.240; 13.Y.175.244; 13.Y.240.228; 13.Y.240.229; 13.Y.240.230; 13.Y.240.231; 13.Y.240.236; 13.Y.240.237; 13.Y.240.238; 13.Y.240.239; 13.Y.240.154; 13.Y.240.157; 13.Y.240.166; 13.Y.240.169; 13.Y.240.172; 13.Y.240.175; 13.Y.240.240; 13.Y.240.244; 13.Y.244.228; 13.Y.244.229; 13.Y.244.230; 13.Y.244.231; 13.Y.244.236; 13.Y.244.237; 13.Y.244.238; 13.Y.244.239; 13.Y.244.154; 13.Y.244.157; 13.Y.244.166; 13.Y.244.169; 13.Y.244.172; 13.Y.244.175; 13.Y.244.240; 13.Y.244.244;

Prodrugs of 14.AH

14.AH.4.157; 14.AH.4.158; 14.AH.4.196; 14.AH.4.223; 14.AH.4.240; 14.AH.4.244; 14.AH.4.243; 14.AH.4.247; 14.AH.5.157; 14.AH.5.158; 14.AH.5.196; 14.AH.5.223; 14.AH.5.240; 14.AH.5.244; 14.AH.5.243; 14.AH.5.247; 14.AH.7.157; 14.AH.7.158; 14.AH.7.196; 14.AH.7.223; 14.AH.7.240; 14.AH.7.244; 14.AH.7.243; 14.AH.7.247; 14.AH.15.157; 14.AH.15.158; 14.AH.15.196; 14.AH.15.223; 14.AH.15.240; 14.AH.15.244; 14.AH.15.243; 14.AH.15.247; 14.AH.16.157; 14.AH.16.158; 14.AH.16.196; 14.AH.16.223; 14.AH.16.240; 14.AH.16.244; 14.AH.16.243; 14.AH.16.247; 14.AH.18.157; 14.AH.18.158; 14.AH.18.196; 14.AH.18.223; 14.AH.18.240; 14.AH.18.244; 14.AH.18.243; 14.AH.18.247; 14.AH.26.157; 14.AH.26.158; 14.AH.26.196; 14.AH.26.223; 14.AH.26.240; 14.AH.26.244; 14.AH.26.243; 14.AH.26.247; 14.AH.27.157; 14.AH.27.158; 14.AH.27.196; 14.AH.27.223; 14.AH.27.240; 14.AH.27.244; 14.AH.27.243; 14.AH.27.247; 14.AH.29.157; 14.AH.29.158; 14.AH.29.196; 14.AH.29.223; 14.AH.29.240; 14.AH.29.244; 14.AH.29.243; 14.AH.29.247; 14.AH.54.157; 14.AH.54.158; 14.AH.54.196; 14.AH.54.223; 14.AH.54.240; 14.AH.54.244; 14.AH.54.243; 14.AH.54.247; 14.AH.55.157; 14.AH.55.158; 14.AH.55.196; 14.AH.55.223; 14.AH.55.240; 14.AH.55.244; 14.AH.55.243; 14.AH.55.247; 14.AH.56.157; 14.AH.56.158; 14.AH.56.196; 14.AH.56.223; 14.AH.56.240; 14.AH.56.244; 14.AH.56.243; 14.AH.56.247; 14.AH.157.157; 14.AH.157.158; 14.AH.157.196; 14.AH.157.223; 14.AH.157.240; 14.AH.157.244; 14.AH.157.243; 14.AH.157.247; 14.AH.196.157; 14.AH.196.158; 14.AH.196.196; 14.AH.196.223; 14.AH.196.240; 14.AH.196.244; 14.AH.196.243; 14.AH.196.247; 14.AH.223.157; 14.AH.223.158; 14.AH.223.196; 14.AH.223.223; 14.AH.223.240; 14.AH.223.244; 14.AH.223.243; 14.AH.223.247; 14.AH.240.157; 14.AH.240.158; 14.AH.240.196; 14.AH.240.223; 14.AH.240.240; 14.AH.240.244; 14.AH.240.243; 14.AH.240.247; 14.AH.244.157; 14.AH.244.158; 14.AH.244.196; 14.AH.244.223; 14.AH.244.240; 14.AH.244.244; 14.AH.244.243; 14.AH.244.247; 14.AH.247.157; 14.AH.247.158; 14.AH.247.196;

14.AH.247.223; 14.AH.247.240; 14.AH.247.244; 14.AH.247.243; 14.AH.247.247;

Prodrugs of 14.AJ

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14.AJ.247.196; 14.AJ.247.223; 14.AJ.247.240; 14.AJ.247.244; 14.AJ.247.243; 14.AJ.247.247;

Prodrugs of 14.AN

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Prodrugs of 14.AP

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Prodrugs of 14.AZ

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Prodrugs of 14.BF

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Prodrugs of 14.CI

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Prodrugs of 14.CO

14.CO.4.157; 14.CO.4.158; 14.CO.4.196; 14.CO.4.223; 14.CO.4.240; 14.CO.4.244; 14.CO.4.243; 14.CO.4.247; 14.CO.5.157; 14.CO.5.158; 14.CO.5.196; 14.CO.5.223; 14.CO.5.240; 14.CO.5.244; 14.CO.5.243; 14.CO.5.247; 14.CO.7.157; 14.CO.7.158; 14.CO.7.196; 14.CO.7.223; 14.CO.7.240; 14.CO.7.244; 14.CO.7.243; 14.CO.7.247; 14.CO.15.157; 14.CO.15.158; 14.CO.15.196; 14.CO.15.223; 14.CO.15.240; 14.CO.15.244; 14.CO.15.243; 14.CO.15.247; 14.CO.16.157; 14.CO.16.158; 14.CO.16.196; 14.CO.16.223; 14.CO.16.240; 14.CO.16.244; 14.CO.16.243; 14.CO.16.247; 14.CO.18.157; 14.CO.18.158; 14.CO.18.196; 14.CO.18.223; 14.CO.18.240; 14.CO.18.244; 14.CO.18.243; 14.CO.18.247; 14.CO.26.157; 14.CO.26.158; 14.CO.26.196; 14.CO.26.223; 14.CO.26.240; 14.CO.26.244; 14.CO.26.243; 14.CO.26.247; 14.CO.27.157; 14.CO.27.158; 14.CO.27.196; 14.CO.27.223; 14.CO.27.240; 14.CO.27.244; 14.CO.27.243; 14.CO.27.247; 14.CO.29.157; 14.CO.29.158; 14.CO.29.196; 14.CO.29.223; 14.CO.29.240; 14.CO.29.244; 14.CO.29.243; 14.CO.29.247; 14.CO.54.157; 14.CO.54.158; 14.CO.54.196; 14.CO.54.223; 14.CO.54.240; 14.CO.54.244; 14.CO.54.243; 14.CO.54.247; 14.CO.55.157; 14.CO.55.158; 14.CO.55.196; 14.CO.55.223; 14.CO.55.240; 14.CO.55.244; 14.CO.55.243; 14.CO.55.247; 14.CO.56.157; 14.CO.56.158; 14.CO.56.196; 14.CO.56.223; 14.CO.56.240; 14.CO.56.244; 14.CO.56.243; 14.CO.56.247; 14.CO.157.157; 14.CO.157.158; 14.CO.157.196; 14.CO.157.223; 14.CO.157.240; 14.CO.157.244; 14.CO.157.243; 14.CO.157.247; 14.CO.196.157; 14.CO.196.158; 14.CO.196.196; 14.CO.196.223; 14.CO.196.240; 14.CO.196.244; 14.CO.196.243; 14.CO.196.247; 14.CO.223.157; 14.CO.223.158; 14.CO.223.196; 14.CO.223.223; 14.CO.223.240; 14.CO.223.244; 14.CO.223.243; 14.CO.223.247; 14.CO.240.157; 14.CO.240.158; 14.CO.240.196;

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All literature and patent citations herein are hereby expressly incorporated by reference at the locations of their citation. Specifically cited sections or pages of the above cited works are incorporated by reference with specificity. The invention has been described in detail sufficient to allow one of ordinary skill in the art to make and use the subject matter of the following claims. It is apparent that certain modifications of the methods and compositions of the following claims can be made within the scope and spirit of the invention.

In the claims hereinbelow, the subscript and superscripts of a given variable are distinct. For example, R_1 is distinct from R^1.

Claims

We claim:

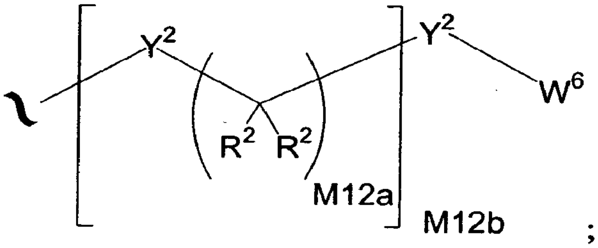
1. A conjugate comprising a kinase inhibiting compound linked to one or more phosphonate groups; or a pharmaceutically acceptable salt or solvate thereof.

2. The conjugate of claim 1, or a pharmaceutically acceptable salt or solvate thereof, that is a compound of any one of formulae **500-511** substituted with one or more groups A^0,

wherein:

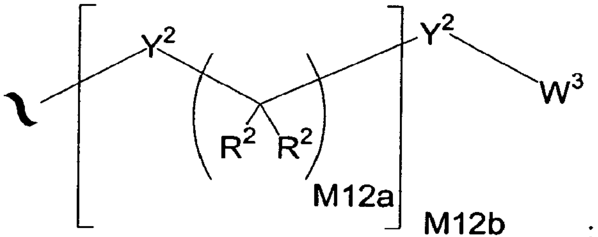
A^0 is A^1, A^2 or W^3 with the proviso that the conjugate includes at least one A^1;

A^1 is:



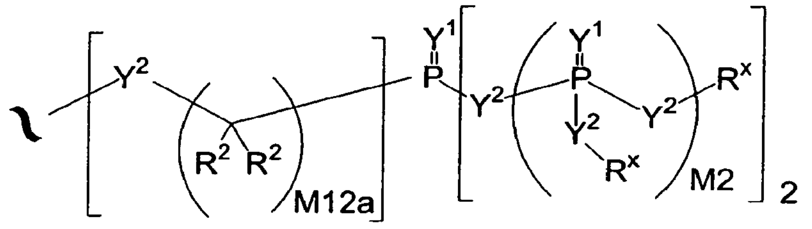
;

A^2 is:



;

A^3 is:

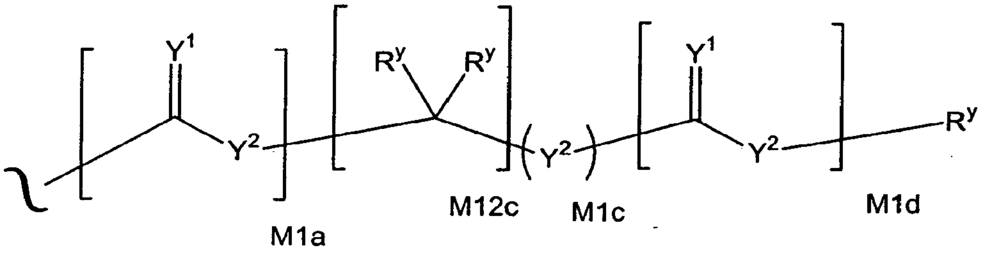


M12b ;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$; and when Y^2 joins two phosphorous atoms Y^2 can also be $C(R^2)(R^2)$;

R^x is independently H, R^1, R^2, W^3, a protecting group, or the formula:



;

wherein:

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_{M2}R^5$, or $-SO_{M2}W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1; and

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

3. The conjugate of claim 2, or a pharmaceutically acceptable salt or solvate thereof, which has the formula:

$$[\text{DRUG}]\text{-}(A^0)_{nn}\ ;$$

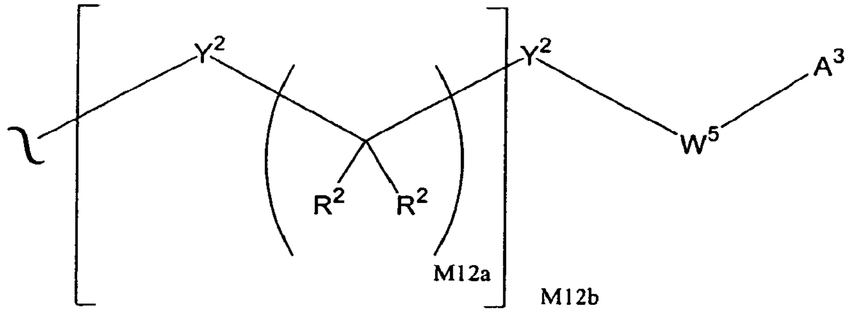
wherein:

DRUG is a compound of any one of formulae **500-511**; and

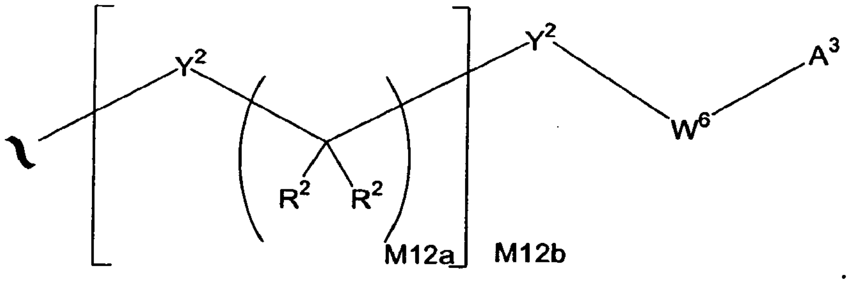
nn is 1, 2, or 3.

4. The conjugate of claim 2 which has any one of formulae **1-36** wherein: one A^0 is A^1; X^{50} is H F, or Cl; and X^{51} is H or Cl.

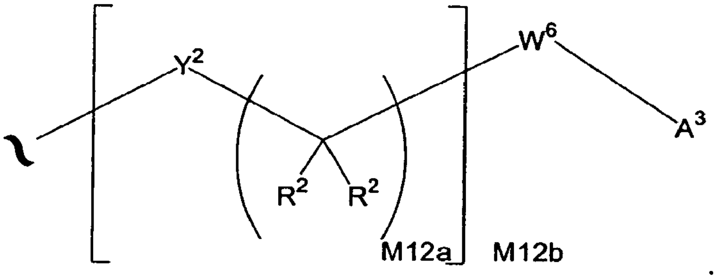
5. The conjugate of claim 2 wherein each A^1 is of the formula:



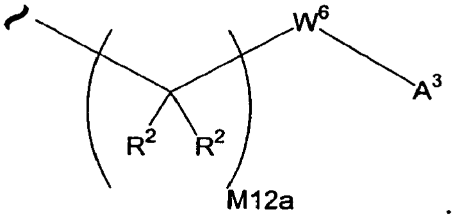
6. The conjugate of claim 2 wherein each A^1 is of the formula:


Y2
R2
R2
M12a
M12b
Y2
W6
A3

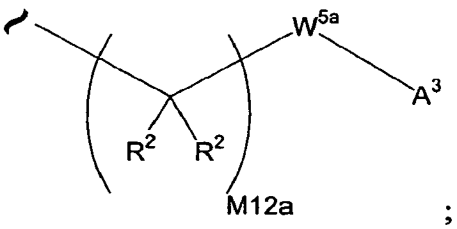
7. The conjugate of claim 2 wherein each A^1 is of the formula:


Y2
R2
R2
M12a
M12b
W6
A3

8. The conjugate of claim 2 wherein each A^1 is of the formula:


W6
A3
R2
R2
M12a

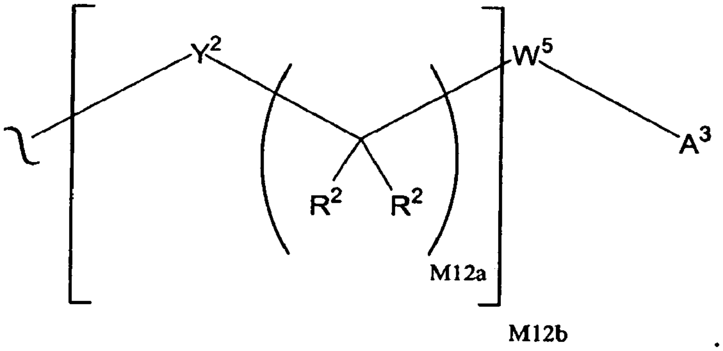
9. The conjugate of claim 2 wherein each A^1 is of the formula:


W5a
A3
R2
R2
M12a

wherein: W^{5a} is a carbocycle or a heterocycle where W^{5a} is independently substituted with 0 or 1 R^2 groups.

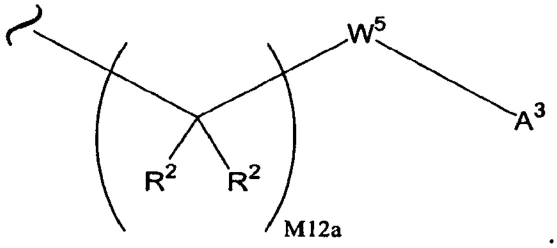
10. The conjugate of claim 2 wherein M12a is 1.

11. The conjugate of claim 2 wherein each A^1 is of the formula:



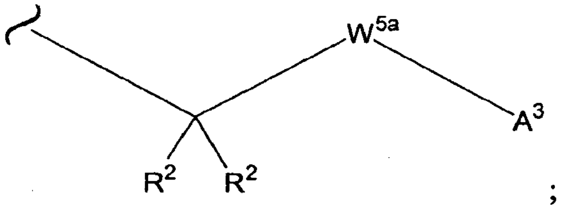
Y^2
W^5
A^3
R^2
R^2
M12a
M12b

12. The conjugate of claim 2 wherein each A^1 is of the formula:



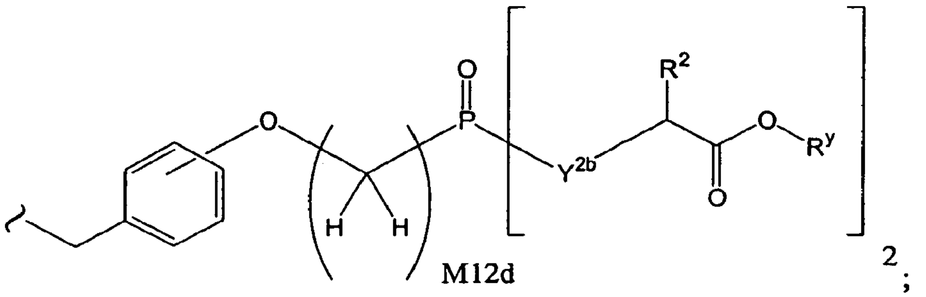
W^5
A^3
R^2
R^2
M12a

13. The conjugate of claim 2 wherein each A^1 is of the formula:



wherein: W^{5a} is a carbocycle independently substituted with 0 or 1 R^2 groups.

14. The conjugate of claim 2 wherein each A^1 is of the formula:


O
P
R^2
O
R^y
Y^{2b}
O
H
H
M12d
2

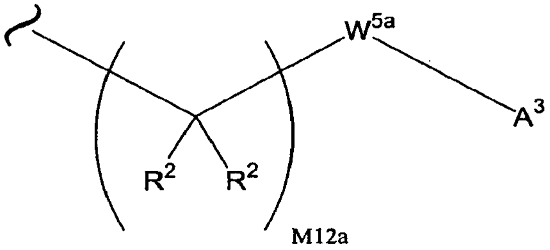
;

wherein:

Y^{2b} is O or $N(R^2)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

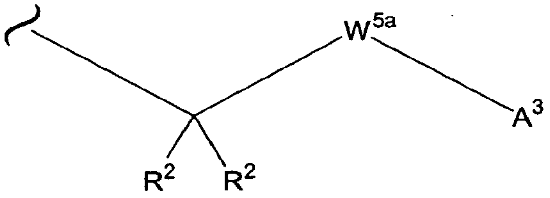
15. The conjugate of claim 2 wherein each A^1 is of the formula:


W^{5a}
A^3
R^2
R^2
M12a

;

wherein: W^{5a} is a carbocycle independently substituted with 0 or 1 R^2 groups.

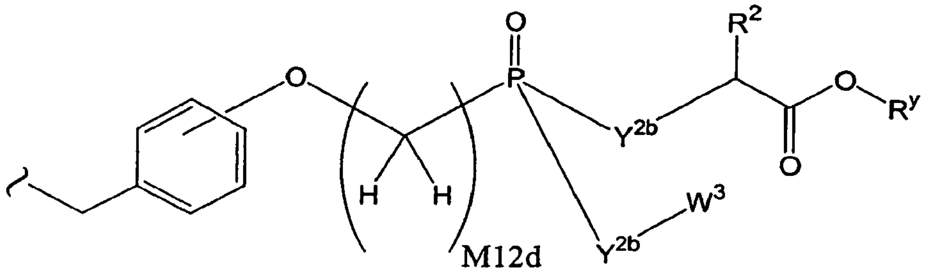
16. The conjugate of claim 2 wherein each A^1 is of the formula:



;

wherein: W^{5a} is a carbocycle or heterocycle where W^{5a} is independently substituted with 0 or 1 R^2 groups.

17. The conjugate of claim 2 wherein each A^1 is of the formula:

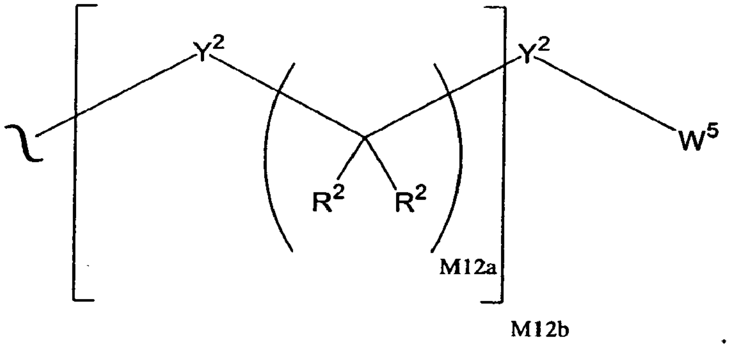

O
P
R²
O
Rʸ
Y²ᵇ
O
H
H
W³
M12d
Y²ᵇ

wherein:

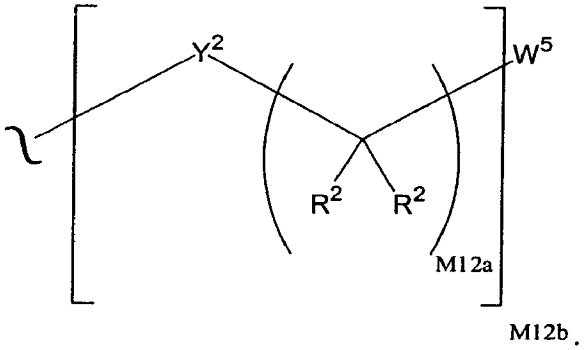
Y^{2b} is O or $N(R^2)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

18. The conjugate of claim 2 wherein each A^2 is of the formula:


Y²
Y²
W⁵
R²
R²
M12a
M12b

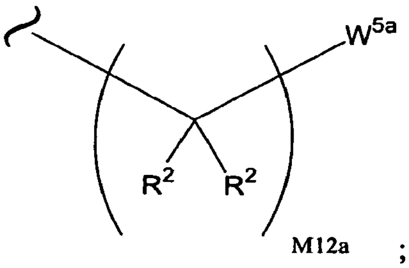
19. The conjugate of claim 2 wherein each A^2 is of the formula:


Y²
W⁵
R²
R²
M12a
M12b

20. The conjugate of claim 2 wherein each M12b is 1.

21. The conjugate of claim 20 where M12b is 0, Y^2 is a bond and W^5 is a carbocycle or heterocycle where W^5 is optionally and independently substituted with 1, 2, or 3 R^2 groups.

22. The conjugate of claim 2 wherein each A^2 is of the formula:



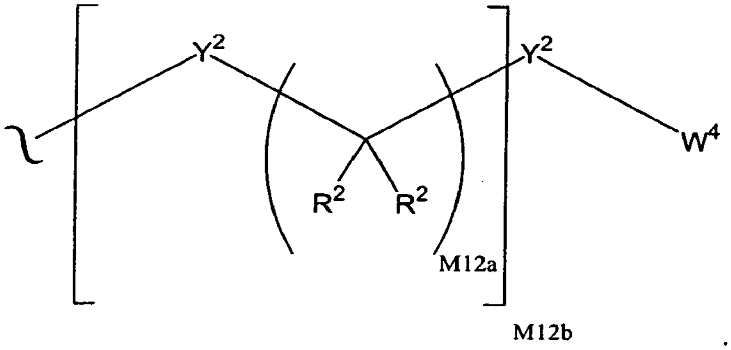
;

wherein: W^{5a} is a carbocycle or heterocycle where W^{5a} is optionally and independently substituted with 1, 2, or 3 R^2 groups.

23. The conjugate of claim 22 wherein M12a is 1.

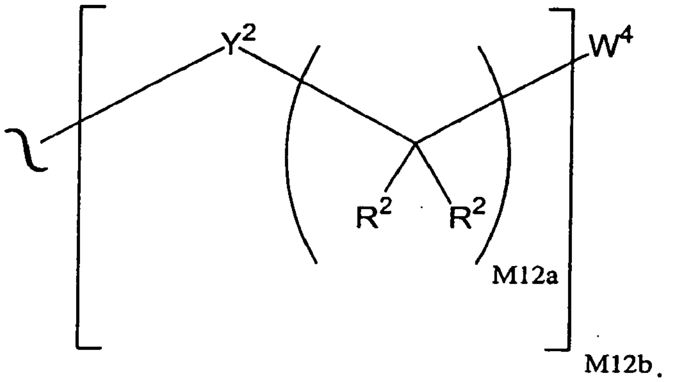
24. The conjugate of claim 2 wherein each A^2 is selected from phenyl, substituted phenyl, benzyl, substituted benzyl, pyridyl and substituted pyridyl.

25. The conjugate of claim 2 wherein each A^2 is of the formula:



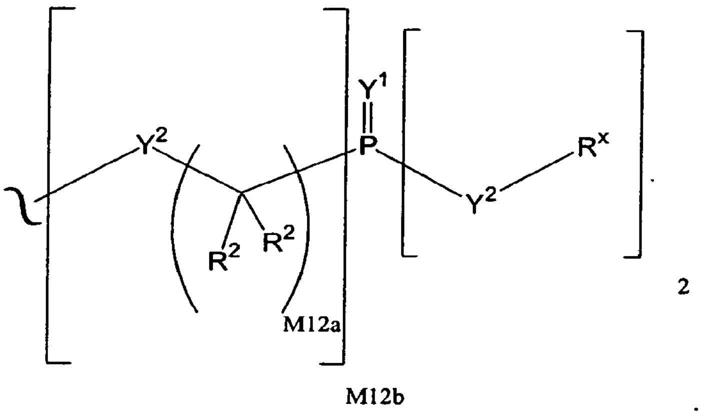
.

26. The conjugate of claim 2 wherein each A^2 is of the formula:

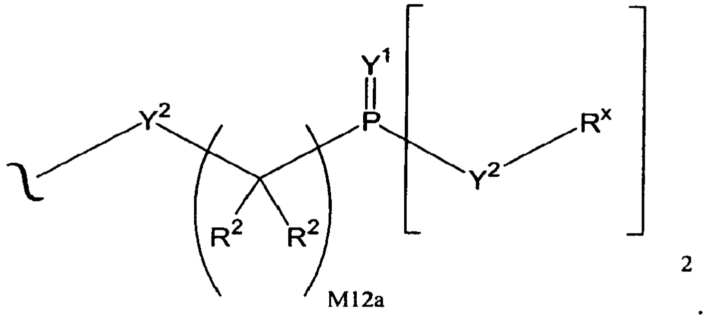

Y2
W4
R2
R2
M12a
M12b.

27. The conjugate of claim 26 wherein M12b is 1.

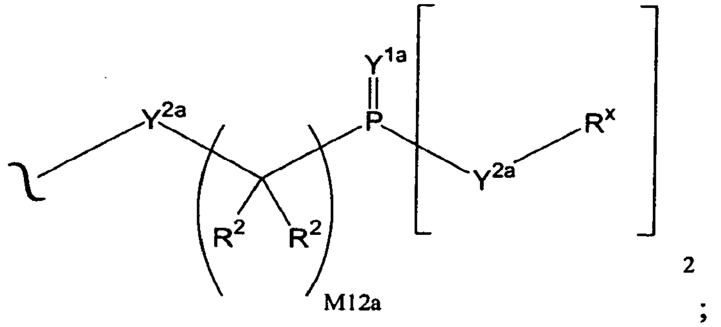
28. The conjugate of claim 2 wherein each A^3 is of the formula:


Y1
Y2
P
Rx
Y2
R2
R2
M12a
M12b
2

29. The conjugate of claim 2 wherein each A^3 is of the formula:


Y1
Y2
P
Rx
Y2
R2
R2
M12a
2

30. The conjugate of claim 2 wherein each A^3 is of the formula:



Y1a
Y2a
P
Rx
Y2a
R2
R2
M12a
2

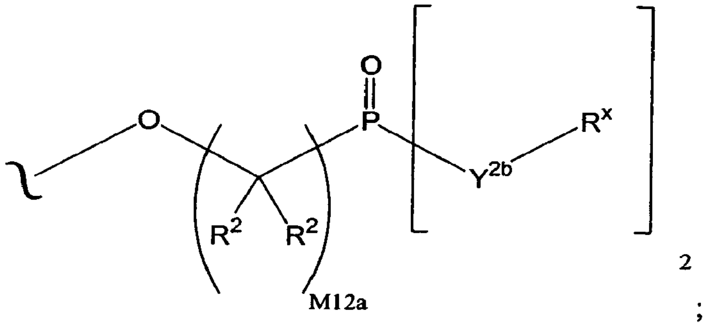
;

wherein:

Y^{1a} is O or S; and

Y^{2a} is O, N(R^x) or S.

31. The conjugate of claim 2 wherein each A^3 is of the formula:

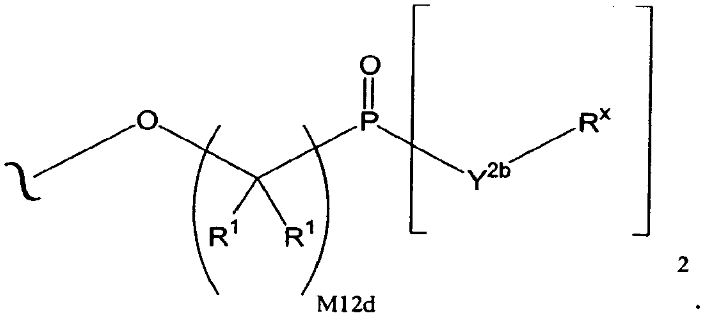


O
O
P
Rx
Y2b
R2
R2
M12a
2

;

wherein Y^{2b} is O or N(R^x).

32. The conjugate of claim 2 wherein each A^3 is of the formula:



O
O
P
Rx
Y2b
R1
R1
M12d
2

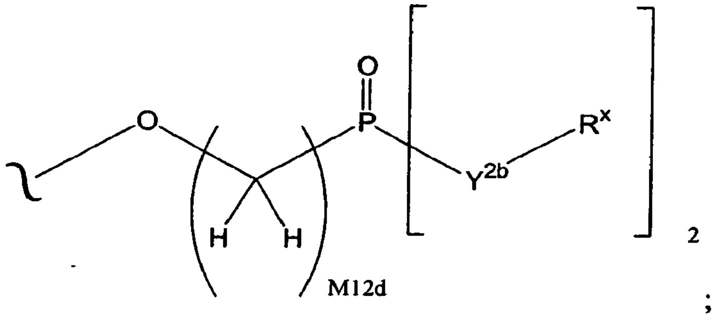
;

wherein:

Y^{2b} is O or N(R^x); and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

33. The conjugate of claim 2 wherein each A^3 is of the formula:


O
O
P
R^x
Y^2b
H
H
M12d
2
;

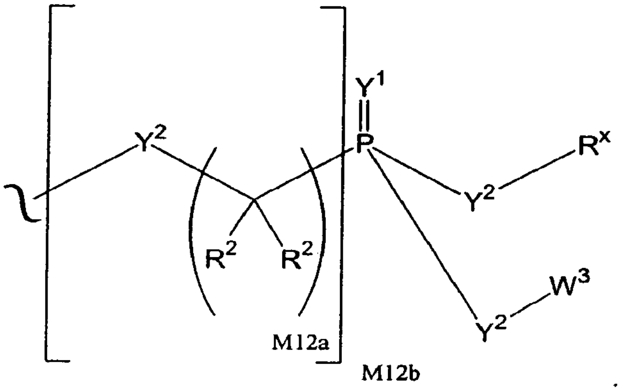
wherein:

Y^{2b} is O or $N(R^x)$; and

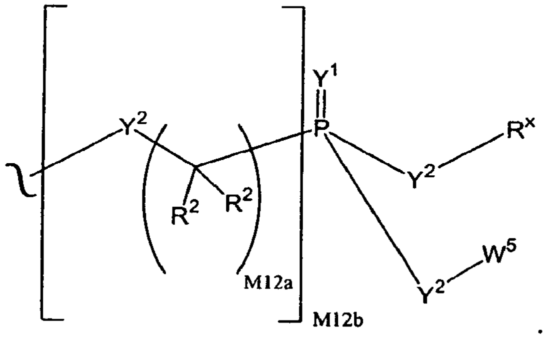
M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

34. The conjugate of claim 33 wherein M12d is 1.

35. The conjugate of claim 2 wherein each A^3 is of the formula:

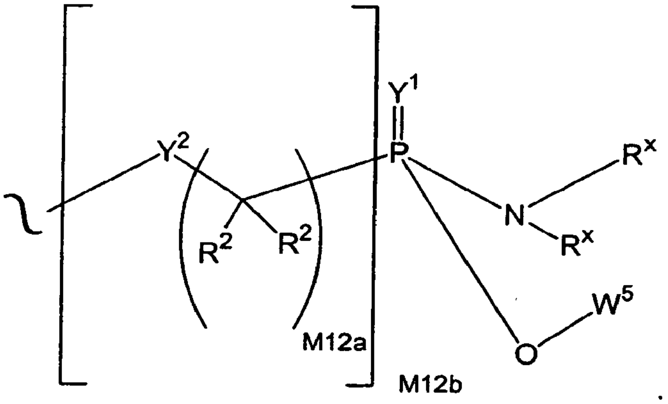

Y1
P
Y2
Y2
R^x
R2
R2
Y2
W3
M12a
M12b

36. The conjugate of claim 2 wherein each A^3 is of the formula:


Y1
P
Y2
Y2
R^x
R2
R2
Y2
W5
M12a
M12b

37. The conjugate of claim 36 wherein W^5 is a carbocycle.

38. The conjugate of claim 2 wherein each A^3 is of the formula:

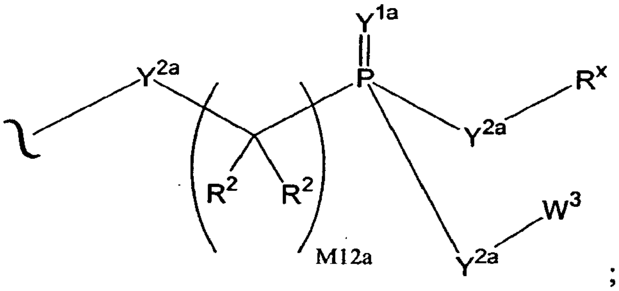


Y1
Y2
P
Rx
N
Rx
R2
R2
W5
M12a
O
M12b

39. The conjugate of claim 38 wherein W^5 is phenyl.

40. The conjugate of claim 39 wherein M12b is 1.

41. The conjugate of claim 2 wherein each A^3 is of the formula:



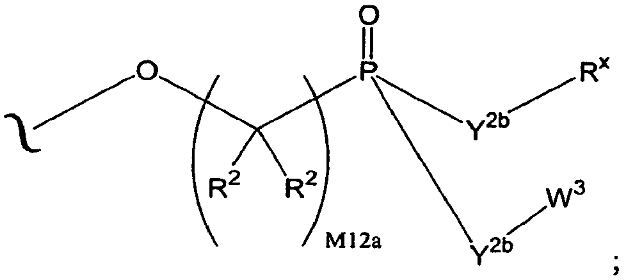
Y1a
Y2a
P
Rx
Y2a
R2
R2
W3
M12a
Y2a

wherein:

Y^{1a} is O or S; and

Y^{2a} is O, $N(R^x)$ or S.

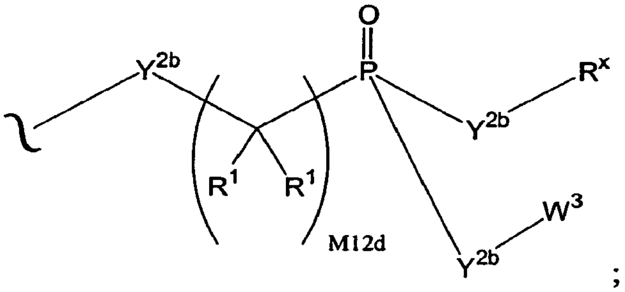
42. The conjugate of claim 2 wherein each A^3 is of the formula:


O
P
O
R^x
Y^2b
R^2
R^2
W^3
M12a
Y^2b

;

wherein Y^{2b} is O or $N(R^x)$.

43. The conjugate of claim 2 wherein each A^3 is of the formula:


O
Y^2b
P
R^x
Y^2b
R^1
R^1
W^3
M12d
Y^2b

;

wherein:

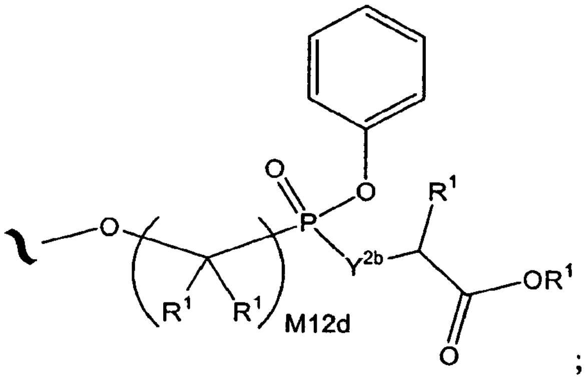
Y^{2b} is O or $N(R^x)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

44. The conjugate of claim 43 wherein R^1 is H.

45. The conjugate of claim 44 wherein M12d is 1.

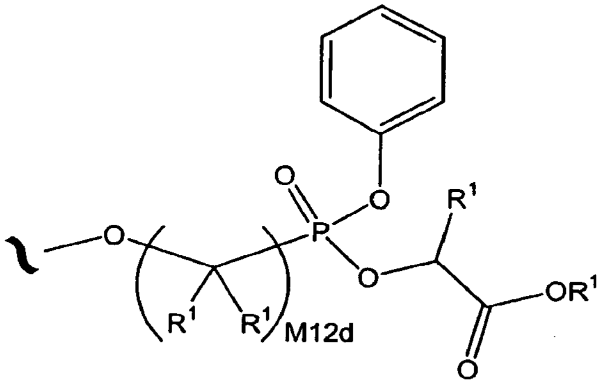
46. The conjugate of claim 2 wherein each A^3 is of the formula:


O
O
R^1
O
P
Y^2b
OR^1
R^1
R^1
M12d
O

;

wherein the phenyl carbocycle is substituted with 0, 1, 2, or 3 R^2 groups.

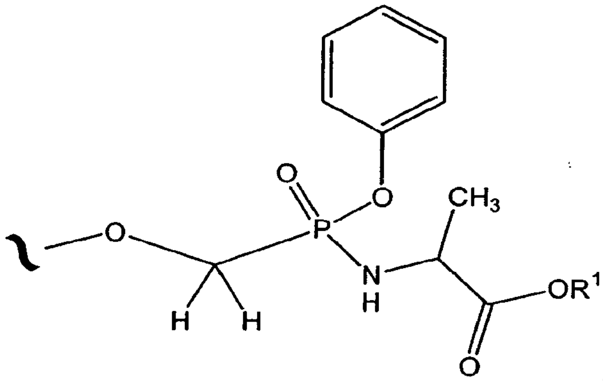
47. The conjugate of claim 2 wherein each A^3 is of the formula:


O
O
P
O
O
R1
R1
R1
M12d
OR1
O

;

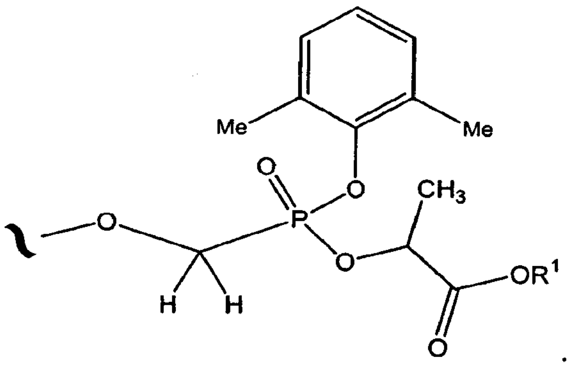
wherein the phenyl carbocycle is substituted with 0, 1, 2, or 3 R^2 groups.

48. The conjugate of claim 2 wherein each A^3 is of the formula:


O
O
P
CH3
O
N
H
H
H
OR1
O

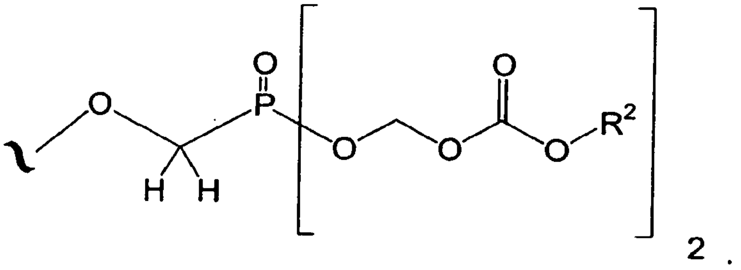
.

49. The conjugate of claim 2 wherein each A^3 is of the formula:

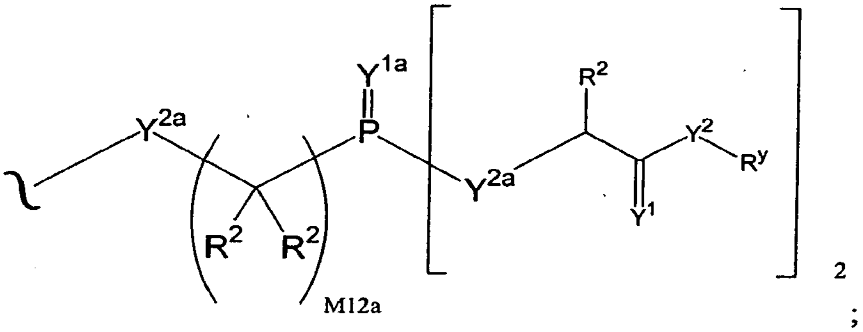

Me
Me
O
O
P
CH3
O
O
H
H
OR1
O

.

50. The conjugate of claim 2 wherein each A^3 is of the formula:


O
O
H
H
P
O
O
O
O
O
R2
2

51. The conjugate of claim 2 wherein each A^3 is of the formula:

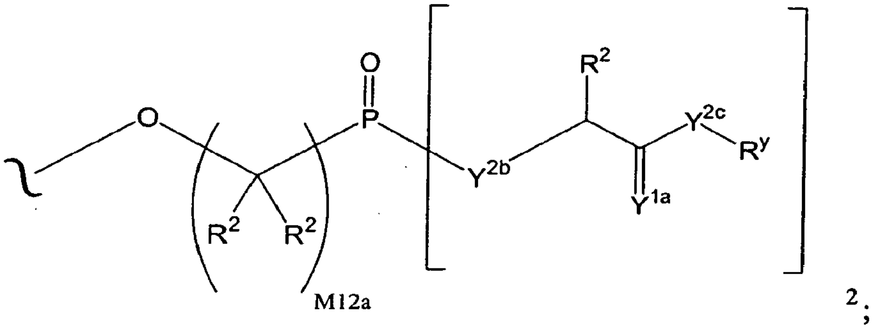

Y1a
P
Y2a
R2
R2
M12a
Y2a
R2
Y2
Ry
Y1
2

wherein:

Y^{1a} is O or S; and

Y^{2a} is O, $N(R^2)$ or S.

52. The conjugate of claim 2 wherein each A^3 is of the formula:


O
P
O
R2
R2
M12a
Y2b
R2
Y2c
Ry
Y1a
2

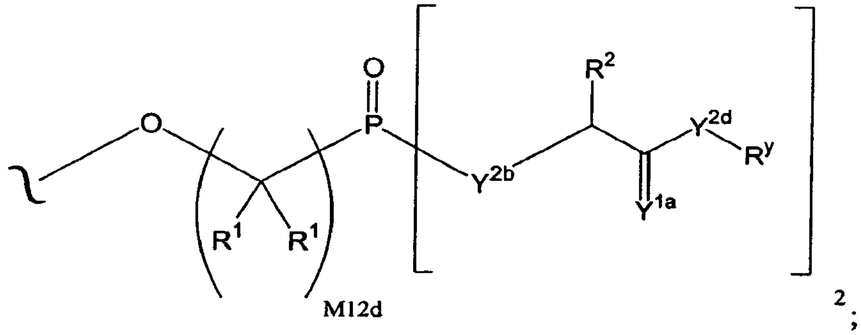
wherein:

Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$; and

Y^{2c} is O, $N(R^y)$ or S.

53. The conjugate of claim 2 wherein each A^3 is of the formula:


O
P
O
R1
R1
M12d
Y2b
R2
Y2d
Ry
Y1a
2
;

wherein:

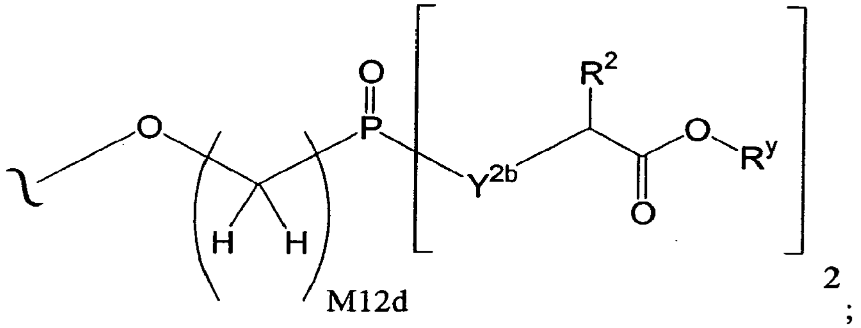
Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$;

Y^{2d} is O or $N(R^y)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

54. The conjugate of claim 2 wherein each A^3 is of the formula:

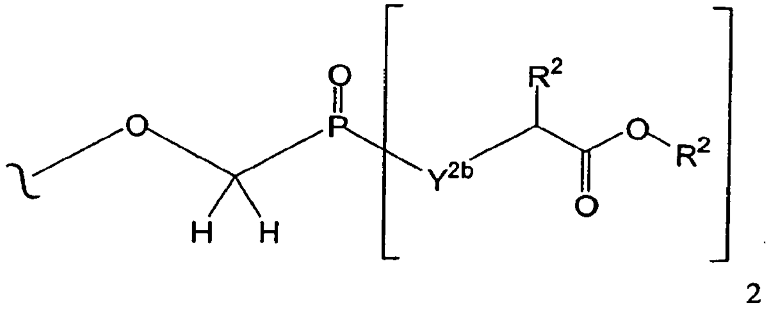

O
P
O
H
H
M12d
Y2b
R2
O
Ry
O
2
;

wherein:

Y^{2b} is O or $N(R^2)$; and

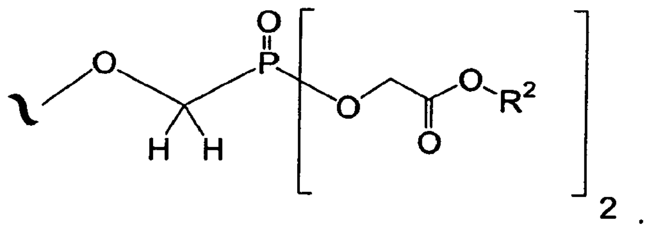
M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

55. The conjugate of claim 2 wherein each A^3 is of the formula:

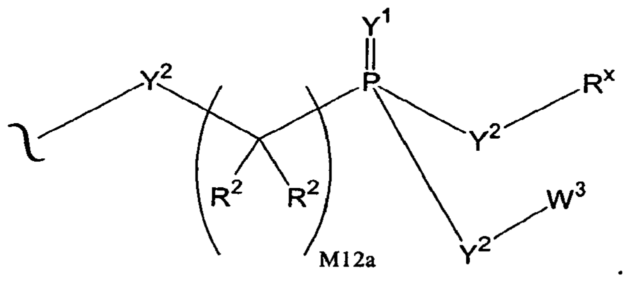


wherein Y^{2b} is O or $N(R^2)$.

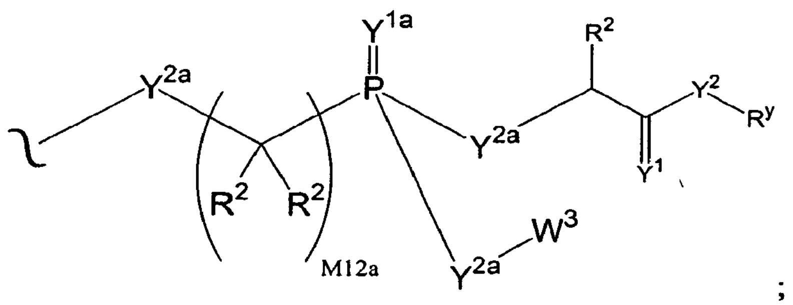
56. The conjugate of claim 2 wherein each A^3 is of the formula:



57. The conjugate of claim 2 wherein each A^3 is of the formula:



58. The conjugate of claim 2 wherein each A^3 is of the formula:



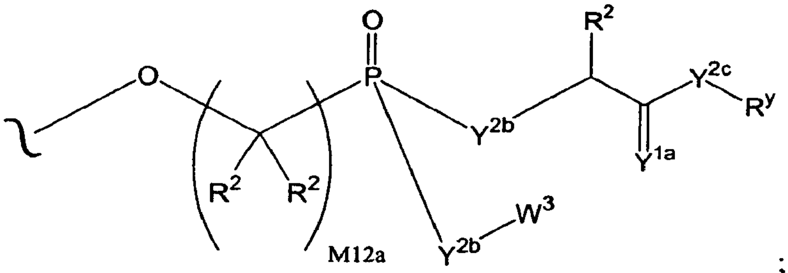
;

wherein:

Y^{1a} is O or S; and

Y^{2a} is O, $N(R^2)$ or S.

59. The conjugate of claim 2 wherein each A^3 is of the formula:



O
P
O
R2
R2
M12a
R2
Y2b
Y2c
Ry
Y1a
Y2b
W3

;

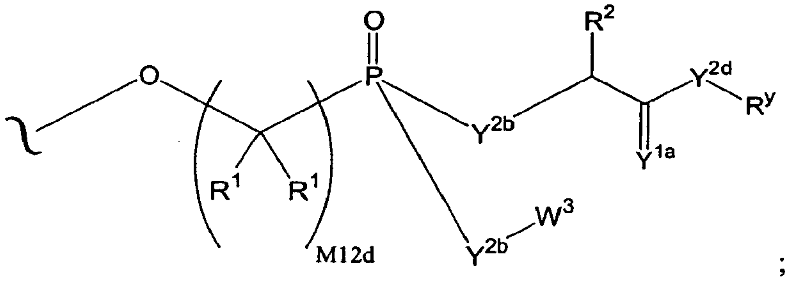
wherein:

Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$; and

Y^{2c} is O, $N(R^y)$ or S.

60. The conjugate of claim 2 wherein each A^3 is of the formula:



O
P
O
R1
R1
M12d
R2
Y2b
Y2d
Ry
Y1a
Y2b
W3

;

wherein:

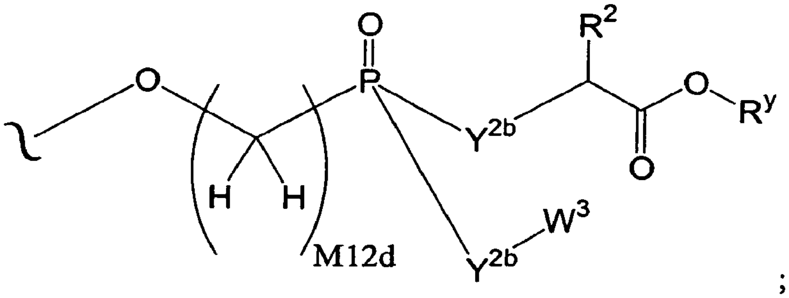
Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$;

Y^{2d} is O or $N(R^y)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

61. The conjugate of claim 2 wherein each A^3 is of the formula:


O
R2
O
RY
P
Y2b
O
H
H
W3
M12d
Y2b

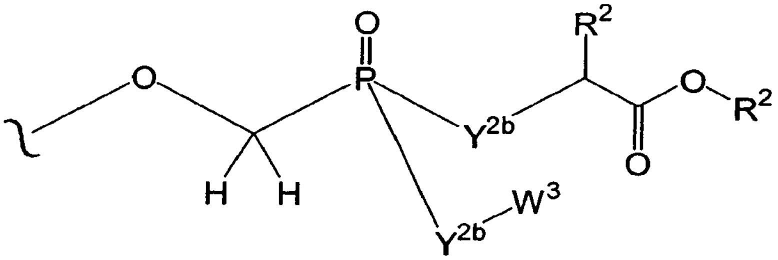
;

wherein:

Y^{2b} is O or $N(R^2)$; and

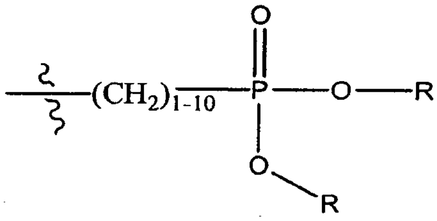
M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

62. The conjugate of claim 2 wherein each A^3 is of the formula:


O
R2
O
R2
P
Y2b
O
H
H
W3
Y2b

wherein Y^{2b} is O or $N(R^2)$.

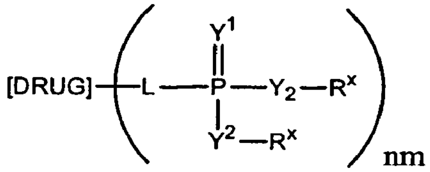
63. The conjugate of claim 3 wherein A^0 is of the formula:


O
(CH2)1-10
P
O
R
O
R

;

wherein each R is independently alkyl.

64. The conjugate of claim 1 which has the formula:



$$[\mathrm{DRUG}]\left(L-\overset{\overset{\displaystyle Y^1}{\|}}{\underset{\underset{\displaystyle Y^2-R^x}{|}}{P}}-Y_2-R^x\right)_{nm}$$

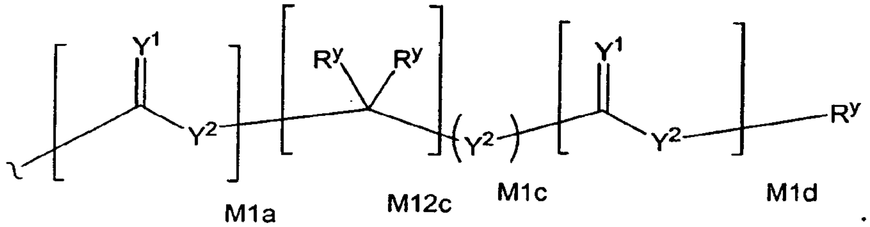
or a pharmaceutically acceptable salt or solvate thereof,
wherein:

DRUG is a kinase inhibiting compound;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$;

R^x is independently H, R^2, W^3, a protecting group, or the formula:



;

R^y is independently H, W^3, R^2 or a protecting group;

R^2 is independently H, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$,
$-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

M2 is 1, 2, or 3;

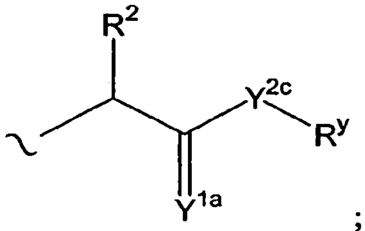
M1a, M1c, and M1d are independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

nn is 1, 2, or 3; and

L is a direct bond or a linking group.

65. The conjugate of claim 64 wherein each R^x is of the formula:



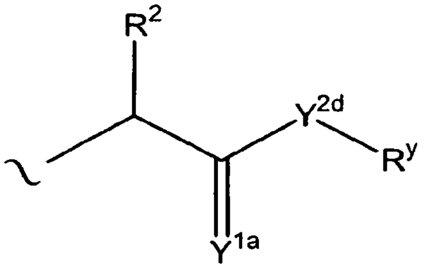
;

wherein:

Y^{1a} is O or S; and

Y^{2c} is O, $N(R^y)$ or S.

66. The conjugate of claim 64 wherein each R^x is of the formula:



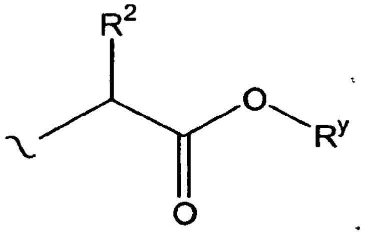
;

wherein:

Y^{1a} is O or S; and

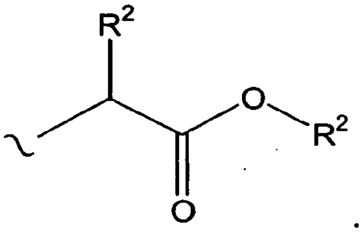
Y^{2d} is O or $N(R^y)$.

67. The conjugate of claim 64 wherein each R^x is of the formula:

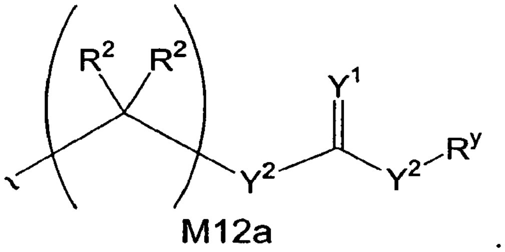


68. The conjugate of claim 64 wherein each R^y is independently H or alkyl of 1 to 10 carbons.

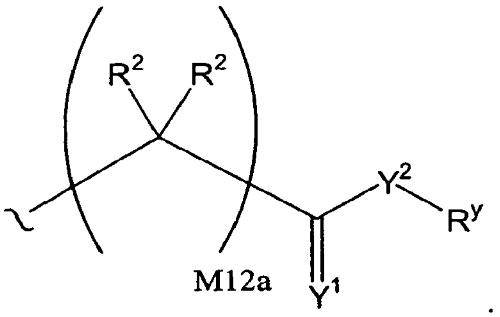
69. The conjugate of claim 64 wherein each R^x is of the formula:



70. The conjugate of claim 64 wherein each R^x is of the formula:


R2
R2
Y1
Y2
Y2
Ry
M12a

71. The conjugate of claim 64 wherein each R^x is of the formula:


R2
R2
Y2
Ry
M12a
Y1

72. The conjugate of claim 64 wherein each Y^1 is O or S.

73. The conjugate of claim 64 wherein each Y^2 is O, $N(R^y)$ or S.

74. The conjugate of claim 64 wherein nn is 1.

75. The conjugate of claim 64 wherein nn is 2.

76. The conjugate of claim 64 wherein nn is 3.

77. The conjugate of claim 64 wherein the kinase inhibiting compound is a compound of any one of formulae **500-511**.

78. The conjugate of claim 77 wherein each L has a molecular weight of from about 20 daltons to about 400 daltons.

79. The conjugate of claim 77 wherein each L has a length of about 5 angstroms to about 300 angstroms.

80. The conjugate of claim 77 wherein each L separates the compound of any one of formulae **500-511** and the phosphorous of the phosphonate group by about 5 angstroms to about 200 angstroms, inclusive.

81. The conjugate of claim 77 wherein each L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 2 to 25 carbon atoms, wherein one or more of the carbon atoms is optionally replaced by (-O-), and wherein the chain is optionally substituted on carbon with one or more substituents selected from (C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo (=O), carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy.

82. The conjugate of claim 77 wherein each L is of the formula W-A wherein A is $(C_1$-$C_{24})$alkylene, $(C_2$-$C_{24})$alkenylene, $(C_2$-$C_{24})$alkynylene, $(C_3$-$C_8)$cycloalkylene, $(C_6$-$C_{10})$aryl or a combination thereof, wherein each W is -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, $-S(O)_2-$, -N(R)-, -C(=O)-, -N(R)C=N(R)-N(R)-, -C(R)=N(R)-, $-S(O)_{M2}-N(R)-$, $-N(R)-S(O)_{M2}-$, or a direct bond; wherein each R is independently H or alkyl of 1 to 10 carbons.

83. The conjugate of claim 82 wherein each A is alkylene of 1 to 10 carbons.

84. The conjugate of claim 77 wherein each L is a divalent radical formed from a peptide.

85. The conjugate of claim 77 wherein each L is a divalent radical formed from an amino acid.

86. The conjugate of claim 77 wherein each L is a divalent radical formed from poly-L-glutamic acid, poly-L-aspartic acid, poly-L-histidine, poly-L-ornithine, poly-L-serine, poly-L-threonine, poly-L-tyrosine, poly-L-leucine, poly-L-lysine-L-phenylalanine, poly-L-lysine or poly-L-lysine-L-tyrosine.

87. The conjugate of claim 77 wherein each L is of the formula $W-(CH_2)_n$ wherein, n is between about 1 and about 10; and W is -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, $-S(O)_2-$, -C(=O)-, -N(R)-, -N(R)C=N(R)-N(R)-, -C(R)=N(R)-, $-S(O)_{M2}-N(R)-$, $-N(R)-S(O)_{M2}-$, or a direct bond; wherein each R is independently H or $(C_1$-$C_6)$alkyl.

88. The conjugate of claim 77 wherein each L is methylene, ethylene, or propylene.

89. The conjugate of claim 77 wherein each L is linked to P at a carbon atom of L.

90. The conjugate as described in claim 1, which is isolated and purified.

91. The conjugate of claim 1 which is not an anti-inflammatory compound.

92. The conjugate of claim 1 which is not an anti-infective.

93. The conjugate of claim 1 which is not a compound that is active against immune-mediated conditions.

94. The conjugate of claim 1 which is not a compound that is active against metabolic diseases.

95. The conjugate of claim 1 which is not an antiviral agent.

96. The conjugate of claim 1 which is not a nucleoside.

97. The conjugate of claim 1 which is not a IMPDH inhibitor.

98. The conjugate of claim 1 which is not an antimetabolite.

99. The conjugate of claim 1 which is not a PNP inhibitor.

100. The conjugate of claim 1 which inhibits a serine/threonine kinase, tyrosine kinase, Bcr-Abl kinase, cyclin-dependent kinase, Flt3 tyrosine kinase, MAP Erk kinase, JAK3 kinase, VEGF receptor kinase, PDGF receptor tyrosine kinase, protein kinase C, insulin receptor tyrosine kinase, or an EGF receptor tyrosine kinase.

101. The conjugate of claim 1 wherein the kinase inhibitor is not Gefitinib, imatinib, erlotinib, vatalanib, alvocidib, CEP-701, GLEEVEC, midostaurin, MLN-518, PD-184352, doramapimod, BAY-43-9006, or CP-690,550.

102. The conjugate of claim 2 which is not a substituted compound of any one of formulae **500-510.**

103. The conjugate of claim 2 which is not a substituted compound of formula **511**.

104. The conjugate of claim 4 which is not a compound of any one of formulae **1-33**.

105. The conjugate of claim 4 which is not a compound of formula **34** or **35**.

106. A kinase inhibitor conjugate as described herein.

107. A compound of the formula MBF.

108. A compound of claim 107 selected from Table 100.

109. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a conjugate as described in claim 1.

110. A unit dosage form comprising a conjugate as described in claim 1 and a pharmaceutically acceptable excipient.

111. A method for inhibiting a kinase *in vitro* or *in vivo* comprising contacting a sample in need of such treatment with a conjugate as described in claim 1.

112. The method of claim 111 wherein the contacting is *in vivo*.

113. The invention also provides a method of inhibiting a kinase in a mammal, comprising administering a conjugate as described in claim 1 to the mammal.

114. The method of claim 113 wherein the conjugate is formulated with a pharmaceutically acceptable carrier.

115. The method of claim 114 wherein the formulation further comprises a second active ingredient.

116. The method of claim 11 wherein the kinase is a serine/threonine kinase, tyrosine kinase, Bcr-Abl kinase, cyclin-dependent kinase, Flt3 tyrosine kinase, MAP Erk kinase, JAK3 kinase, VEGF receptor kinase, PDGF receptor tyrosine kinase, protein kinase C, insulin receptor tyrosine kinase, or an EGF receptor tyrosine kinase.

ABSTRACT

The invention is related to phosphorus substituted kinase inhibitory compounds, compositions containing such compounds, and therapeutic methods that include the administration of such compounds, as well as to processes and intermediates useful for preparing such compounds.

Attorney Docket No. 1692.306US1

SCHWEGMAN ■ LUNDBERG ■ WOESSNER ■ KLUTH

United States Patent Application

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that

I verily believe I am the original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled: **KINASE INHIBITORY PHOSPHONATE ANALOGS**.

The specification of which is attached hereto.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with 37 C.F.R. § 1.56 (attached hereto). I also acknowledge my duty to disclose all information known to be material to patentability which became available between a filing date of a prior application and the national or PCT international filing date in the event this is a Continuation-In-Part application in accordance with 37 C.F.R. § 1.63(e).

I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on the basis of which priority is claimed:

No such claim for priority is being made at this time.

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below:

Application Number	Filing Date
60/465588	April 25, 2003
60/465594	April 25, 2003
60/465465	April 25, 2003
60/465569	April 25, 2003
60/495382	August 15, 2003
60/495685	August 15, 2003
60/495527	August 15, 2003
60/495686	August 15, 2003
60/513956	October 24, 2003
60/513925	October 24, 2003
60/514368	October 24, 2003
60/514207	October 24, 2003
60/514115	October 24, 2003
60/514324	October 24, 2003
60/513974	October 24, 2003

60/514330	October 24, 2003
60/531932	December 22, 2003
60/536054	January 12, 2004

I hereby claim the benefit under 35 U.S.C. § 120 or 365(c) of any United States and PCT international application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose material information as defined in 37 C.F.R. § 1.56(a) which became available between the filing date of the prior application and the national or PCT international filing date of this application:

No such claim for priority is being made at this time.

I hereby appoint the following attorney(s) and/or patent agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith:

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I hereby authorize them to act and rely on instructions from and communicate directly with the person/assignee/attorney/firm/organization/who/which first sends/sent this case to them and by whom/which I hereby declare that I have consented after full disclosure to be represented unless/until I instruct Schwegman, Lundberg, Woessner & Kluth, P.A. to the contrary.

Please direct all correspondence in this case to **Schwegman, Lundberg, Woessner & Kluth, P.A.** at the address indicated below:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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§ 1.56 Duty to disclose information material to patentability.

(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

(1) prior art cited in search reports of a foreign patent office in a counterpart application, and

(2) the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentably defines, to make sure that any material information contained therein is disclosed to the Office.

(b) Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and

(1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or

(2) It refutes, or is inconsistent with, a position the applicant takes in:

(i) Opposing an argument of unpatentability relied on by the Office, or

(ii) Asserting an argument of patentability.

A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

(c) Individuals associated with the filing or prosecution of a patent application within the meaning of this section are:

(1) Each inventor named in the application:

(2) Each attorney or agent who prepares or prosecutes the application; and

(3) Every other person who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application.

(d) Individuals other than the attorney, agent or inventor may comply with this section by disclosing information to the attorney, agent, or inventor.